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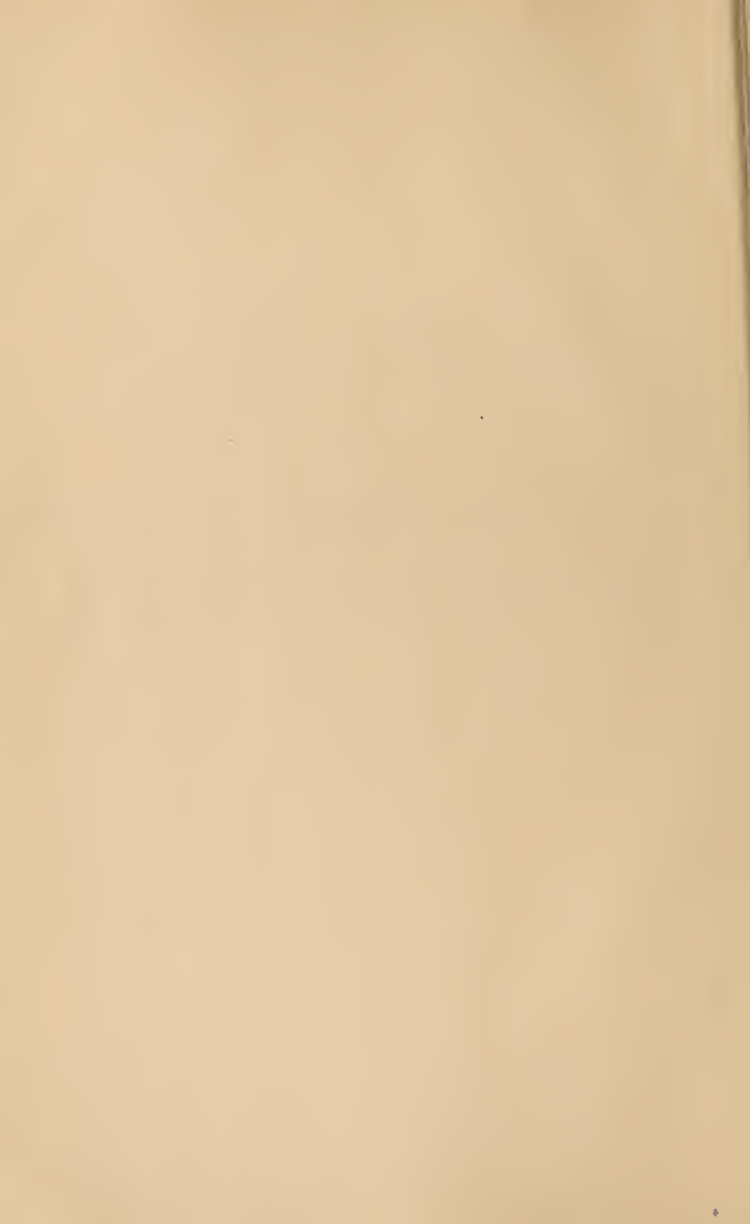
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TO  
DR. HIRAM N. VINEBERG

A PIONEER IN HIS CHOSEN FIELD

THIS VOLUME IS DEDICATED

ON THE OCCASION OF HIS EIGHTY-FIFTH BIRTHDAY

AS A TOKEN OF ESTEEM

AND AS AN EXPRESSION OF APPRECIATION,

AFFECTION AND GOOD WISHES

BY HIS FRIENDS, ASSOCIATES AND PUPILS



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FOR MAKING POSSIBLE THE DEDICATION OF THIS  
SPECIAL ISSUE OF THE JOURNAL  
TO DR. HIRAM N. VINEBERG  
EMERITUS GYNECOLOGIST  
WHO HAS GIVEN THIRTY-ONE YEARS OF VALUABLE  
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*Airam H. Vinberg*



## FOREWORD

It is a great privilege, and a greater personal satisfaction, to be allowed to write the Foreword to this Anniversary Volume which is to convey to DR. HIRAM N. VINEBERG, the esteem and affectionate greetings of his many colleagues, friends, former pupils and associates. This tribute is due him not merely for his professional achievements which are outstanding, but above all for his high (the highest) ethical standards, for his sincere devotion to the welfare of his patients, and to the physicians working with and under him.

Born with the instincts of a true gentleman, he could not and did not do otherwise. Some of his earliest testimonials from his teachers and from the laity speak of his high standards in the profession and of his unselfish devotion to the interests of those placed under his care.

Everyone of us might envy him his early experiences. He may well be proud of the claim that he is "a self-made man." Some think well of themselves because they improved every opportunity offered them; Vineberg created his own opportunities. At fifteen years he left home ("had to dig for myself"), worked hard, and at nineteen years had saved enough to enter the medical school of McGill University, taking the four year course and achieving all sorts of distinction, receiving a gold medal for "highest marks recorded for many years." He began practice in Montreal in April 1878. For reasons of health and to satisfy a roving spirit, he became a ship's doctor, visiting Liverpool, London and finally reaching New Zealand (in a sailing vessel). Sometime later he landed at Honolulu, was appointed by King Kalakaua, doctor in charge of a district on the island of Oahu; was asked to accept a position as Attending Physician of the leper settlement on Molokau where he got in touch with the illustrious Father Damien. Possibly Stevenson heard of our friend. All this, and no doubt much more, he kept to himself all these years. Drop your modesty, friend Vineberg, and during your leisure hours, write a full account of those years. Steal a march on your biographer.

Special acknowledgement is due Dr. Vineberg for his splendid influence on the younger gynecologists. Several of his loyal pupils bear testimony to this. By his rigid adherence to highest scientific standards, he was recognized as one of the ablest diagnosticians in his special sphere. He had the courage to admit openly an occasional error, and was far removed from a small but conspicuous group of those early, and these later years, who in consultation, would "rather be learned than be right." One of his ablest followers assures me that Vineberg was a great teacher, extraordinarily scrupulous in advising for, or against, operation, placing the welfare of the patient above all else. No wonder he compelled the admiration of William Osler, who was his teacher and lifelong friend. All his professors, in special testimonials, stressed his ability—"able physician and an honorable upright man"; "enthusiastic and upright man." No wonder the passengers on the Western Monarch, in a testimonial<sup>1</sup> dated at Wellington, New

<sup>1</sup> The original is worth preserving as a museum piece.

Zealand, January 2, 1880, expressed their high esteem of the young doctor as a professional man, and as a true gentleman. The lady passengers were especially grateful and devoted.

The present writer has known Vineberg since the day he began practice in New York (well over fifty-five years ago). It was his ambition to succeed in a great city. From the very start, he was the true gentleman in speech and bearing. It was not always smooth sailing (it never is); he met some unfriendly criticism with great dignity. He had the will to succeed, and the push. He achieved the goal of every high-minded physician: the sincere devotion of his patients, sincere friendships among his colleagues, and a reputation for extreme honesty in his relations to his fellow men and fellow workers. In short, Hiram N. Vineberg proved himself to be a friend of mankind, a great physician, a genuine American. May he "add to his years, but stop counting them." Enjoy the glories of a life well spent.

BERNARD SACHS

GUILLAUME MAUQUEST DE LA MOTTE-HIRAM  
NAHUM VINEBERG

PALMER FINDLEY, M.D.

*[Omaha, Nebraska]*

GUILLAUME MAUQUEST DE LA MOTTE (1655-1737). It would seem a far cry from Guillaume Mauquest de la Motte to Hiram Nahum Vineberg, as indeed it is in point of time. Yet in one particular there is a similarity that challenges our interest—both came at the dawn of a new era in the gynecologic science, one in the old world, the other in the new.

La Motte lived in a period of intellectual awakening when midwifery was being molded into a science out of the common clay of superstition, ignorance and religious bigotry. No longer chained to a dead past, in which all intellectual liberty was stifled by the clergy, La Motte was free to pursue his scientific investigations untrammelled by religious dogma and the superstitious beliefs of midwives who for ages had exercised a dominating influence on the practice of midwifery.

World-shaking events had taken place in this period commonly referred to as the Renaissance. Columbus had discovered a new world, John Gutenberg had invented the printing press. Martin Luther had founded Protestantism, Isaac Newton had revealed the true nature of the solar system, Shakespeare and Milton had made their priceless contributions to classical literature, Leonardo da Vinci had revealed in graphic form the true attitude of the fetus in utero, Rembrandt had painted "The Anatomie" at a time when dissection of the human body was under the ban of the Church, William Harvey had followed the course of the blood through the heart, Leeuwenhoek had invented the microscope, Malpighi had laid the foundation for histology, Paré had made revolutionary contributions to surgery and William Hunter was pursuing his anatomic studies in preparation for his immortal thesis on the anatomy of the gravid uterus.

These events, and more, were the heritage of La Motte, but there was more to inspire in him that zeal for scientific research that made for him an exalted place in the annals of obstetrics—there were men in his own time who were making their contributions to a new science. In his own country was Francis Mauriceau of whom it is said "he drew from the cradle the art of midwifery," there was Paul Portal who doubtless inspired La Motte in the employment of conservative measures in delivery as did Philippe Peu. Van Deventer of the Hague contributed to his knowledge of the bony pelvis at a time when there were no instruments for the accurate measurement of the bony pelvis, and there was John Harvie in London who antedated Credé by nearly a century in formulating "practical directions showing the method of preserving the perineum and delivering the placenta without violence." Unfortunately the Chamberlens withheld the secret of their iron "tongs" and it was left to William Smellie and Chap-

man to popularize the obstetric forceps, though it is not known that La Motte ever possessed an obstetric forceps.

La Motte was born in 1655. He served for a period of five years as an externe in the Hotel Dieu of Paris and it was there that he became interested in obstetrics. For thirty years he was engaged in the general practice of medicine in the village of Picardy at Balognes where as a general practitioner his skill in the art of delivery gained for him world-wide fame. Of his daily routine he wrote:

As I live at the tip end of a province bounded on nearly every side by the sea, and as I usually work in the country, without physicians and surgeons who might aid me with their advice, or who, at least, are very rarely to be found, I have been obliged to conduct myself usually in endeavoring to aid Nature and to control the accidents which accompany pregnancy and labor, all the more so that good sense and my reflections have furnished me with the means, without submitting me too much to the authorities, nor rendering me a slave to the customs generally received, unless I recognize the necessity of conforming myself to them on account of the disease, the constitution of the patients, and other circumstances from which one may draw certain considerations.

La Motte possessed no obstetric forceps, no pelvimeter, no antiseptic, no anesthetic, no hospital accommodations, yet he boasted that he was always successful in ending labor without resort to forceps, crochet or other instruments. Necessity made him self-reliant and resourceful and above all, his isolation led him to rely upon nature's forces rather than upon artificial means. It is said that he was remarkably clever in performing podalic version and only twice in his life did he resort to scissors and crochet and then only after assuring himself that the child was dead. He expressed the hope that the time would come when the impacted head could be extracted by instruments of iron but when Palfyn of Gent produced such an instrument, claiming that with it the wedged-in head of the child could be extracted without injury to either mother or baby, La Motte was skeptical. Said he, "If Palfyn's instrument would not do what he claims for it, worms should eat his intestines for eternity, but if it proves to be all he claims for it his name should be blessed for all time." He argued that under such circumstances the blade of the instrument could no more pass the side of the head than a cable could be passed through the eye of a needle.

La Motte was not befuddled by the superstitious beliefs that had plagued midwifery for thousands of years. He did not believe in maternal impressions, he refuted the age-old belief that a fetus delivered in the seventh month of gestation had a better chance of survival than one delivered in the eighth month, yet he did subscribe to the prevailing notion that the baby came into the world on its own power. While he combatted the ancient theory that the moon regulated the menstrual cycle he did accuse a red-headed maid of serving him white wine while menstruating, causing the wine to turn red and sour.

La Motte, at the age of 72, published a thesis entitled *Traite Complet des Accouchemens, etc.*, 1722. It was in no sense a monumental contribution, such as was produced by Mauriceau at about the same period, but it abounded in practical, common sense aphorisms and historical citations, such as would be expected of a man of La Motte's years and experience. The work was largely

a recital of his reflections after a lifetime of obstetrical practice under circumstances that tried his ingenuity. Throughout the entire text there is found a note of confidence in the author's ability to overcome all obstacles.

Witness such comments as: "I delivered as quickly and easily as taking a handkerchief from my pocket"—"The child escaped from the vulva as readily as an eel slips through your hands"—"The child was delivered in less time than needed to recite a *Pater* and an *Ave*."

In this treatise we find a detailed description of La Motte's technique in "turning by the foot" and his method of dilating the introitus to forestall injuries to the pelvic floor. Here the author dwells at length on the contracted pelvis and the technique of delivery in obstructed labor. He was the first to recognize the pelvic inlet as a factor in dystocia—this is probably his most important contribution to the development of the obstetric science. "History," says the historian Fasbender, "will record a prominent place for La Motte in the doctrine of the narrow pelvis."

In La Motte's time it was common practice to bleed the expectant mother to facilitate delivery but La Motte would have none of it, though he did confess to having drawn blood seventeen times in a prolonged labor. He took issue with Mauriceau and Van Deventer in what he regarded as unwarranted resort to scissors and hooks, contending that in his practice delivery had been accomplished without the use of these instruments and with less pain, less cruelty and greater safety to the mother and child. Said he, "The Lord has given me the means of extracting living children if called in time and without the employment of murderous instruments."

La Motte performed podalic version in placenta previa and eclampsia as well as in contracted pelvis. He laid great emphasis upon the advisability of abiding the time when moulding of the fetal head would permit the passage of the head through a contracted birth canal. Only in extreme cases did he admit of failure when sufficient time was given to accomplish the moulding of the fetal head.

Just what virtue La Motte found in vinegar applied to the abdomen in uterine hemorrhage is not clear. While he never performed a cesarean section he recognized the justifiability of resorting to the hazardous procedure under exceptional circumstances. It is remarkable that such an exponent of conservation should endorse the procedure at a time when cesarean operations were attended by such an appalling maternal mortality. In his time the maternal mortality following cesarean section approached one hundred per cent and was decried by nearly all authorities to the time when antiseptics and anesthetics were employed in obstetric practice.

Of La Motte's treatise Parvin said, "It is one of the professional treasures the well-educated physician will not neglect. The work, *Traite des Accouchemens*, is a monument to the industry, the knowledge and skill of a practitioner who for more than half a century, in a comparatively obscure part of the country, faithfully toiled, not to gain riches or fame, or to secure a place in hospital or college, but for the glory of the Creator and the relief of man's estate."

La Motte's writings were not confined to obstetrics. Dr. Tiessinger writes

that in the village of Thoirett the books of one Dr. Bichat were stored in an attic of an innkeeper. When found they were covered with cobwebs and among them was a treatise on surgery by La Motte. In this treatise, found as late as 1889, we find La Motte was well abreast of the times in the field of general surgery. Avoiding, with commendable discretion, the brain and the abdomen he performed the usual operations then in vogue. It is said that among his patients were Countesses, Marques and the aristocracy.

The good sense of the author is revealed in the following quotation: "When the effect of a remedy which reason indicates to us hasn't all the success which one expects that is not a reason to reject it absolutely, especially when it is justified by other experiences. But one must as soon as possible examine the causes which prevented its success for nature varies so much in its different operations that very often what is good for one patient is exactly opposite for another although both appear attacked by the same disease."

HIRAM NAHUM VINEBERG. In presenting the above biographical sketch of a man whose genius won for him a place with Mauriceau, Van Deventer and Justine Siegemundin of the seventeenth century as a founder of the modern gynecological science I am reminded that it was given to Hiram N. Vineberg the opportunity of contributing in no small part to the building of a superstructure upon the foundation laid by the past masters.

Hiram N. Vineberg prepared for his life's work the hard way. Born in an unknown village near Kovno, Russia, he does not know the exact date of his birth (probably December 20, 1857). His father was a lumber merchant in Russia, his mother died from a post partum hemorrhage in giving birth to Hiram and his twin sister. The father married soon after the death of his first wife and shortly thereafter he left his family to seek his fortune in Canada. A year later his wife and three children joined him in a little village located about twenty miles north of Cornwall, Ontario. There Hiram grew to his fifteenth year when he left home to engage in a small mercantile business in the village of Forester's Falls, Ontario. When eighteen years of age he disposed of his business and after a six months' period of instruction by an English tutor, he matriculated in McGill University and received his degree of Doctor of Medicine at the end of the prescribed four-year course. In the third year of his medical course he was awarded a prize for scholarship and in his fourth year the Holmes Gold Medal was awarded him in recognition of the high marks he obtained in written and clinical examinations.

"I began practice in Montreal in April, 1878," writes Dr. Vineberg, "and was doing very well for a beginner but my health was not very good and the future outlook was not promising; the roving spirit seized me and at the end of eighteen months, I left Montreal." Then followed six years in which he circumnavigated the globe. First to Liverpool, then to London where he walked the wards for three months. Receiving an appointment as ship doctor he went by Clipper to Wellington, New Zealand, then to Honolulu by steamer and for a year he was Doctor-in-Charge of three sugar plantations on the Island of Oahu and medical

attendant of the natives, covering a district of about thirty miles. Returning to Montreal he located in general practice in Portage la Prairie, Ontario where he remained for three years. There he acquired a liking for gynecology and obstetrics and to fulfill his ambition to specialize he quit his practice and spent the following year in the clinics of Berlin, Vienna and Prague.

Now a gynecologist and obstetrician in his own right he located in New York City, January, 1886. Of necessity he did general practice for several years while getting his bearings in his chosen specialty. First an assistant to Dr. James B. Hunter, in the Polyclinic Hospital, and later as assistant to Dr. George M. Edebohls, in the Post-Graduate Hospital, he came into his own in 1894 when he was appointed Chief of Staff in the Out-Patient Department of The Mount Sinai Hospital. In 1910 he was advanced to Associated Attending Gynecologist, in 1916 to full Attending of The Mount Sinai Hospital and remained in this position until 1921 when he was retired, having reached the "age limit." He was then placed on the Consulting Staff for life.

Dr. Vineberg became a Fellow of the American Gynecological Society in 1897 and an Honorary Fellow in 1929. He was First Vice President in 1925. In this time he contributed thirteen papers to the Transactions of the Society and forty-two papers to various other Societies—an almost unprecedented number. He was formerly an Instructor in the New York Polyclinic and Post-Graduate Hospitals, and Gynecologist-In-Chief in the Beth Moses Hospital. In 1917, he was President of the New York Obstetrical Society.

Never having been intimately associated with Dr. Vineberg in his day-by-day activities, I asked a member of the Attending Staff of The Mount Sinai Hospital to give me an appraisal of Dr. Vineberg as a man and surgeon. Here, in substance, is his reply:

"A master technician, unexcelled in clinical judgment. Though not trained in pathology, he had acquired a familiarity with morbid tissues that led him to judge with uncanny certainty their nature and clinical significance. As a man he possessed absolute intellectual integrity. While at times brusque in his statements, and at the expense of diplomatic finesse, he was equally free in self-criticism and thus gained the respect and admiration of his colleagues. His candid admissions of his own limitations were a constant source of inspiration to the younger members of the Staff."

Well may Dr. Hiram N. Vineberg say with Cato: "The greatest comfort of my old age and that which gives me the highest satisfaction is the pleasing remembrance of the many benefits and friendly offices I have done to others."

# DATES AND EVENTS IN THE SCIENTIFIC CAREER OF

## DR. HIRAM N. VINEBERG



Entered McGill University as a student in the Medical Faculty.....	1874
Received M.D., C.M. degree, McGill University.....	1878
Awarded Holmes Gold Medal by Medical Faculty of McGill University..	1878
Post-graduate student in Internal Medicine, London.....	1880
Post-graduate student in Gynecology and Obstetrics, Berlin, Danzig, Prague and Vienna.....	1885
Appointed to Out-Patient Internal Female Department, The Mount Sinai Hospital.....	1890
Chief, Out-Patient Gynecological Department, The Mount Sinai Hospital.	1893
Attending Gynecologist, Montefiore Hospital.....	1894
Founder of New York Graduate Society, McGill University.....	1895
Adjunct* Gynecologist, The Mount Sinai Hospital.....	1900
President, New York Graduate Society, McGill University.....	1905
Consulting Gynecologist, Montefiore Hospital.....	1908
Attending Gynecologist, The Mount Sinai Hospital.....	1916
President, New York Obstetrical Society.....	1917
Chief Gynecologist, Beth Moses Hospital, Brooklyn.....	1919
Consulting Gynecologist, The Mount Sinai Hospital.....	1921
First Vice-President, American Gynecological Society.....	1925
Consulting Gynecologist, Beth Moses Hospital, Brooklyn.....	1929

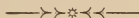
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\* The title of "Adjunct Attending" was equivalent to that of "Associate" today. In 1911 the title of "Adjunct Attending" became "Associate" and "Assistant Adjunct Attending" became "Adjunct."

DR. HIRAM N. VINEBERG

RECEIVES

THE HOLMES GOLD MEDAL



The Holmes Gold Medal is awarded by the Medical Faculty of McGill University to the graduate who achieves the highest marks both in the primary examination at the end of three years and the final examination at the end of four years. Dr. Hiram N. Vineberg received the Medal on March 28, 1878, having earned the highest marks that had been previously recorded for many years.

There is an interesting incident associated with the event. The written examinations at the end of both terms occurred on Saturdays. Dr. Vineberg, who was then a scrupulous observer of the Jewish faith, found himself in an awkward dilemma. He went to the Principal, Sir William Dawson, and explained to him the situation. It so happened that Sir William was a religious man himself, and respected Dr. Vineberg's scruples. He said he would grant a special written examination on the following Monday, but it would need to be more difficult than the previous one on Saturday, so as not to create any dissatisfaction among the rest of the class. Furthermore, he could not compete for the Primary Prize. However, so high were the marks Dr. Vineberg attained, that he was awarded the prize. Thereafter the written examinations took place on Monday instead of Saturday.

ADDRESS AT THE PRESENTATION OF A SILVER CUP TO DR.  
HIRAM N. VINEBERG, ON THE OCCASION OF HIS RETIREMENT  
AS ATTENDING GYNECOLOGIST AT THE MOUNT SINAI HOSPI-  
TAL, MARCH 19, 1921, BY

SOLOMON WIENER, M.D.

It is my pleasant duty, acting as spokesman for your former House Surgeons of The Mount Sinai Hospital, to address a few words to you upon the occasion of your retirement from active duty on the Attending Staff of the Hospital.

We realize that it is still a far cry from writing "*finis coronat opus*" to your career; that you are still full of "pep," and that many years of fruitful activity lie ahead of you. We rejoice in that fact. Nevertheless it would ill become us to let this occasion pass without a few words expressive of our esteem and affection.

Those of us familiar with your professional career are filled with admiration at the success you have achieved. Coming to New York a stranger to its professional life, you have by your own unaided efforts won to a position of eminence which few of us can hope to equal. It is no exaggeration to say that you have achieved a national reputation. Any word of yours is sure of close and respectful attention in any gathering of the elite of your chosen speciality. In this city your name is a household word in gynecology.

One of the many charming addresses of your life-long friend, Sir William Osler, is entitled "The Master Word in Medicine." That master word he states is work. It has indeed been your master word. Your untiring zeal, sir, your unflagging interest in your work has been, and is, an inspiration to every-one of us.

A few weeks ago, upon the occasion of your making your last ward rounds, a large number of your former house surgeons gathered to accompany you and do their little bit to show you honor. In the few words of appreciation you spoke at that time you expressed some surprise and your gratification that so many were present in spite of the fact that, as you said, you were critical in your work, and not an easy man to assist. Why, sir, of whom pray were you ever more critical than of yourself and of your own work? This is one of your many qualities which we have learned to love, which has won for you our respect, and our gratitude for the lesson it has taught.

Over the entrance to the operating room of one of the large European gynecological clinics is inscribed this motto: "*Qui bene diagnoscit, bene curat.*" This is the keynote of your success, this is the most valuable lesson you have taught us, and for it we are profoundly grateful.

As a slight material token of our sentiments, we ask you, sir, to accept this cup. The law of the land may make it difficult for you to fill it with what were considered the proper ingredients in the good old days gone by, but we hand it to you full to the brim with the richest elements of the wine of life—with honor, esteem, gratitude, and affection.

# DR. HIRAM N. VINEBERG—HIS CONTRIBUTIONS TO THE SCIENCE AND ART OF SURGERY

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# CLINICAL DATA ON CHORIO-EPITHELIOMA WITH END-RESULTS OF OPERATIVE TREATMENT<sup>1</sup>

HIRAM N. VINEBERG, M.D., F.A.C.S.

[*New York*]

There probably is no more interesting topic in the whole domain of gynecology than that of chorio-epithelioma. An entirely physiological process, by slightly over-stepping its bounds, becomes, at once, a highly malignant condition with rapid and extensive metastases. Although it is generally associated with gestation, it may, nevertheless, occur in individuals in whom pregnancy can positively be excluded, as, for example, in a very young female, or in a male. Its development, under these conditions, forms a most interesting chapter in pathology. Another curious feature is its occasional development, originally in areas more or less remote from the site of the ovular implantation, while this remains free from the process. These and several other points in the pathology of the condition form a very tempting topic, but as they have already been so fully discussed in the literature by distinguished and capable pathologists, the writer felt it would be more within his powers to take up the clinical side, which, until now, has been very much neglected. His contribution upon this aspect of the subject is based upon nine personal cases and upon a close and rather extensive study of the literature. It is generally agreed that there are two varieties of chorio-epithelioma, the one highly malignant, the other semi-benign. The chief interest to us as clinicians is: Are there any means of distinguishing the one from the other? Marchand, who undoubtedly is the greatest authority upon the subject, and who, as we all know, has done so much to establish its pathology, frankly confesses he has failed to recognize any histological differences between the two varieties. A few pathologists, however, notably V. Velits, Robert Meyer and Ewing, have attempted to point out features of differentiation, but their observations have not been confirmed by others. Several eminent pathologists, whom the writer has personally interviewed, emphatically stated they were unable to recognize any histological differences. The consensus of opinion, therefore, at present is that there are no definite histological features characterizing the one variety from the other.

## FREQUENCY

The number of cases recorded in the literature has been variously stated. For instance, Péry, in 1910, stated there were 700 cases on record. He has been frequently quoted. The figures are entirely too high. Pollosson and Violet, in 1913, made a very careful collection of the recorded cases and they accept Briquel's collection, in 1903, of 217 cases. From that date until 1913, they collected

<sup>1</sup> Read before the American Gynecological Society, Philadelphia, May 17, 1918.

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238 more cases, making in all 455 cases. From 1913 up to the end of 1917, the writer has found recorded in the literature 69 cases which with his series of 9 cases make a total of 78 cases. Of course, it must be borne in mind that during this period the literature coming to us from Germany and Austria has been very scant.

#### ETIOLOGY

With very few exceptions, pregnancy has preceded the development of the growth; it is, therefore, essentially a disease of fertile women. But, as Teacher states, whether race, climate, or social conditions exert any influence upon its occurrence, we do not, at present, know. The ages at which it has occurred have varied from 17 to 55 years. In the series of 189 cases tabulated by Teacher in 1903, the average age was 33 years, 57 per cent of the total number occurred between the ages of 20 and 40 years, but there were 6 cases below 20 and 9 cases over 50 years.

In the writer's series of 78 cases, 4 were under 20 years; 13 were between 20 and 25; 21 were over 40 years, of these 8 were 50 and over.

The number of cases below 20 years and over 50 years is of great interest, and undoubtedly has some bearing upon the fact that hydatid mole which is the most frequent cause of the growth, is more often met with at the extremes of fertile life. Another factor of interest is that the frequency of the disease runs parallel with the degree of fertility.

In 156 cases of Teacher's series, in which the necessary data were available, 5 per cent occurred in connection with the first pregnancy, 15 per cent with the second pregnancy, 28 per cent with the second or third pregnancies. On the other hand, Briquel's 158 cases in his series of 181, give a much higher percentage with the second and third pregnancies: 33, or 21 per cent, with the second pregnancies; 31 or 20 per cent, with the third pregnancies; and 74, or 47 per cent, with the fourth or more pregnancies.

It is interesting to note the period elapsing between the last pregnancy and the development of the disease; in other words, the period of latency. This very often is not easily defined, as it usually has to be based upon the occurrence of the first symptom, which is generally hemorrhage, or upon the appearance of a characteristic tumor in the vagina or vulva.

The period of latency, in the cases recorded has varied from a few weeks to several years; the longest period stated is 21 years.

Many writers doubt the accuracy of the long period of latency stated in several cases. They assume that a miscarriage of an early gestation had been overlooked. Be that as it may, there are some cases with incontrovertible evidence that several years elapsed between the last possible gestation and the development of the growth. Such a case is reported by Kroesing (1). The patient was 52 years of age; 5½ years before, the uterus had been emptied of a hydatid mole; 2¼ years later, both ovaries were removed. At this time the uterus looked perfectly normal. Following the operation there was a complete cessation of the menses, 3¼ years later, and 5½ years after the hydatid molar pregnancy, the uterus was removed for metrorrhagia and was found to be the seat of chorio-epithelioma.

Bearing upon this point, Emil Ries, of Chicago (2) has made a most interesting and unique observation. In a uterus containing several fibroids that he removed from a woman who had not been pregnant for 18 years, he noticed a long thread-like formation hanging from the left uterine horn. This, on microscopic examination, proved to be a vein containing degenerated chorionic villi. No chorionic epithelia were found on these villi, which, according to Dr. Ries, would account for the non-development of chorio-epithelioma in that instance. The finding demonstrated beyond a question, the long period (in this instance 18 years), during which chorionic villi may remain latent in the system.

There cannot be much doubt that in many of the cases reported with a latent period of a few weeks, the growth had already existed before the termination of the pregnancy. In our Case 8, the growth was detected with the exploring finger, after manually emptying the uterus of a hydatid mole. Similar cases are reported by Eden (3) Kelly and Workman (4). In Pick's (5) famous case, the growth in the vagina developed during the presence of a hydatid mole in the uterus (fourth month of gestation). Wallart reported a metastatic growth in the eighth month of pregnancy. Von Rosthorn, Poter and Wasmer, each observed a metastatic growth in the vagina before the expulsion of a hydatid mole. The case reported by Jellinghaus (6) evidently belonged to this class. The patient was curetted for a hydatid mole. She continued to bleed, was again curetted and then subjected to a hysterectomy, five weeks after the first curettage. A growth was found in the uterus. Jellinghaus, in the writer's opinion, evidently failed to recognize the significance of the course of events in his case, otherwise he would not make the recommendation that every case of hydatid mole should be subjected to a second curettage, three weeks after the first, to ascertain whether any cystic villi are present, and if found, hysterectomy should be done.

But the treatment of hydatid mole, in reference to chorio-epithelioma, will receive attention later on. Bovée (7) reports an interesting case in this connection. In a fibroid tumor of the uterus, complicated with pregnancy, which he removed, a chorio-epitheliomatous growth was accidentally found in the wall of the uterus.

A most important consideration is the nature of the pregnancy preceding the disease. In Teacher's series of 188 cases, 73 cases, or 35 per cent, followed hydatid mole; 59 cases, or 31 per cent, followed abortion; 49 cases, or 28 per cent, followed labor at or about term; 7 cases, or 4 per cent, followed extra-uterine gestation.

In Pollosson and Violet's series of 455 cases, including Briquel's series of 217 cases, 203 cases, or 45 per cent, followed hydatid mole; 135 cases, or 30 per cent, followed abortion; 99 cases, or 21 per cent, followed labor at term; 12 cases, or 2.5 per cent, followed extra-uterine gestation; 6 were doubtful.

In Hitschmann and Cristofolletti's series of 240 cases, 116 cases, or 48 per cent, followed hydatid mole; 73 cases, or 30 per cent, followed abortion; 51 cases, or 21 per cent, followed normal labor.

They also give statistics of 200 cases of hydatidiform mole, of which 15 or 7.5 per cent were followed by chorio-epithelioma. Teacher is of the opinion that this

figure is too high; as five of the cases were recorded by Kromer, and as they all recovered after operation, he is inclined to question the validity of the diagnosis of malignancy. Omitting these cases of Kromer, the percentage is 5, which Teacher thinks is still too high.

### *Symptomatology*

The most characteristic and prominent symptom is uterine hemorrhage. This, as a rule, is very profuse and may even be alarming, as occurred in one of my cases (Case 1). The second hemorrhage was so great that the patient became markedly exsanguinated in a few minutes, and it appeared to me, she would have bled to death, if I had not at once packed the uterus and vagina tightly with gauze.

However, in many instances, the bleeding may be only of moderate amount, but protracted, simulating that which accompanies ordinary placental or decidual residue. As a rule, the patient is subjected to a curettage, but it is found that the bleeding soon recurs. This of itself should excite suspicion. But it is not uncommon to read in the literature of cases that had been subjected to as many as four or five or six curettages, before the condition was suspected. The persistence and, at times, very abundant bleeding soon lead to marked anemia, with its train of symptoms, cachexia becomes manifest, the patient feels and looks ill, and a septic condition may intervene. The latter is particularly prone to occur when several curettages have been done. This occurred in one of the writer's cases (Case 7), the only fatal one in the series.

In growing the tumor occasionally perforates the uterus; then there may be a most profuse intraperitoneal hemorrhage, simulating ruptured tubal pregnancy of the cataclysmic type. T. Wilson (8) reports a case of this kind and few others are found in the literature. In very rare instances, even when the growth is situated at the placental site, bleeding may be entirely absent, as in a case reported by Lichtenstein (9). Even amenorrhea of three or four months duration has been observed in a few cases (Eden, Cataruni, and others). This singular phenomenon has been observed only in cases following hydatid mole. Pollosson and Violet (10) draw attention to the presence of colic-like pains, caused by the expulsion of blood clots or of debris of the growth. A dull pain is an accompaniment of the later stages of the disease, when the broad ligament becomes involved. Hemoptysis is an important symptom and may manifest itself comparatively early in rapidly advancing cases. It usually indicates the presence of pulmonary metastases (Teacher). In some instances, when the symptoms, referable to the genital tract, were not distinct or absent, a diagnosis of pulmonary phthisis was made.

In many cases, an early evidence of the disease is the appearance of characteristic tumors in the vaginal walls, most frequently in the anterior wall, near the urethral meatus. These may vary in size from that of an almond to that of a hen's egg. When they attain the latter size they are usually single. They possess a deep bluish color and appear very vascular. In other instances, several small papules will appear in the vaginal walls, preferably on the posterior wall,

corresponding in size to that of a split pea. They have the characteristic bluish appearance and seem as if they were situated beneath the vaginal mucosa. The uterus is usually found enlarged, the degree of enlargement varying from that corresponding to the gravid organ at six weeks, to that at twelve weeks. The cervical canal may be patulous, readily admitting the index finger, thus permitting an exploration of the cavity. The growth then will be felt as a hard nodule of variable size, with a distinct excavation in the center. When it can positively be concluded that the excavation had not been artificially produced by a previous curettage, one is safe in making the diagnosis of chorio-epithelioma. In one of the writer's cases (Case 8) he was able to reach the correct diagnosis on the strength of this finding, even in the face of a negative report by the pathologist, from an examination of the curetted material. But not infrequently the uterus may not be appreciably enlarged, the growth being of very small dimensions, as has been recorded in several cases in the literature. The writer, in his series, met with one instance, in which the growth was no larger than a cherry, and was situated beneath the peritoneal covering, near the left cornu, the uterus, in that instance naturally, not being perceptibly enlarged.

In some of the cases recorded in the literature, there was an entire absence of symptoms referable to the genital tract, the first manifestation of the disease being symptoms due to a cerebral or spinal tumor, or to pulmonary metastasis. A. Straume (11) reports a case diagnosed as pulmonary tuberculosis, on account of hemoptysis, dyspnea, and pain in the chest. There was no bleeding from the genitals, neither was there a history of a hydatid mole, abortion, or labor at term.

A. Kedrierski (12) reports a case in which paraplegia developed eight months after last delivery at term. At the autopsy a chorio-epitheliomatous growth was found in the spinal cord, at the level of the fourth lumbar vertebra. Similar growths were found in the lungs, liver, and both ovaries. The uterus and vagina were entirely free of growths.

#### CHORIO-EPITHELIOMA IN CONNECTION WITH ECTOPIC PREGNANCY

There are 13 cases recorded in the literature of chorio-epithelioma in the tube. The resulting mass has varied in size from that of a hen's egg to that of an adult head. The tumor is very friable and exceedingly hemorrhagic. The histological features are the same as those of chorio-epithelioma of the uterus. Metastases are very frequent. Chorio-epithelioma of the tube has always been a discovery at operation, or on autopsy. It seems to have a more rapid course and a more rapid extension than chorio-epithelioma of the uterus.

#### ECTOPIC GROWTHS

While the usual site of chorio-epithelioma is in the body of the uterus, the growth has developed primarily in other situations. Sternberg (13) reported a case in which the growth involved the vaginal portion of the cervix, the remainder of the uterus being free of any growth. The endometrium showed a decidual reaction. The last pregnancy ending in an abortion, occurred 7 years before.

## METASTASES

Metastases in chorio-epithelioma are of very frequent occurrence. They appear at a varying period and sometimes occur at a very early stage. In the case of Poten and Vassmer, two vaginal tumors were excised five days before the presence of a chorio-epithelioma was detected in the uterus. Metastases have been observed in nearly all the organs. In these cases the metastases take place through the blood-current. Most commonly a fragment of the neoplasm enters the blood current, passing through the heart, and arrives in the lungs where it is disseminated to all the organs. But in the case of the organs in the genital sphere the metastases reach them through the venous anastomosis of the pelvic organs.

Robert Proust and Xavier Bender in their very excellent paper on chorio-epithelioma have presented a very full description of metastases, to which I am indebted for many of the following data.

Metastases in the lungs are most frequent and their number and size vary very much. Occasionally only one tumor is found which may acquire very large dimensions, or more frequently numerous small nodules are found scattered over the entire lung. The most favorable sites are the apices and the bases. The middle lobes are less frequently involved. These metastases may develop insidiously and give no evidence of their presence until found at autopsy. This absence of clinical evidence is dependent upon the site, number, and volume of the secondary growths.

In the case of Lindfors (14) and Morison (15) the secondary growths developed to a relatively enormous size.

Next to the lungs, the vagina and vulva are the most frequent sites of metastatic growths. On account of their situation they are the most easily discerned. Occasionally a single isolated tumor only is present, but more frequently there are numerous small nodules running together forming almost a ring. Their form and their dimensions are most variable as also their location. They may involve the entire vaginal canal or they may occur only at the vulvar orifice or in the folds of the labia majora. They usually occur in the form of small nodular masses underneath the mucosa characterized by their brown or violet discoloration. They have been justly compared to thrombosed varices which they resemble so closely as to be frequently mistaken for them. The consistency is tense and elastic, almost fluctuating at times. These tumors grow very rapidly, causing necrosis and irregular ulcerations. Occasionally these ulcerations are clean cut and well defined. The vaginal growths when they undergo ulcerations may be attended with profuse and obstinate hemorrhages. They very soon become infected and give rise to a sanious and fetid discharge. The period of the appearance of the vaginal metastases varies considerably. Occasionally they appear in the later stages of advanced cachexia, but in some cases they occur remarkably early and furnish a valuable diagnostic sign.

*Uterine ligaments, tubes, ovaries.* The broad ligament is frequently found infiltrated by nodular masses of smaller or larger size. The invasion of the tubes and ovaries is occasionally characterized by small discrete growths dis-

covered only on histological examination. At other times the growths may reach a considerable size readily distinguished by their reddish brown or dark color and their hemorrhagic aspect on section.

*Liver.* Secondary growths in the liver are frequently found at autopsy. Generally the nodules are found disseminated, of a size varying from that of a pea to a small nut. In a case reported by Hitschmann, the entire liver was literally riddled with metastatic nodules. Paviot observed a case in which there was a tumor 4 centimeters in diameter on the convex surface and a large number of other growths in the depth of the liver. These metastatic growths generally do not give rise to many symptoms. Krawer and Macaggi have noted an increase in the volume of the liver, but the existence of a secondary tumor the size of a fetal head was not even suspected in a case of Schmorl's.

*Kidneys, urinary passages.* Nitzel, Tibaldi Gottschalk, and many others have observed secondary growths in the kidneys, but the growths usually remained latent. In a case of Davis and Harris, a tumor in the left kidney 6 centimeters in diameter did not give rise to a single symptom. The exception occurred in a case of Gottschalk in which the urine contained characteristic plasmodial masses. In this instance, it is true, the tumor attained the size of a fetal head. Secondary growths have very rarely been observed in the ureter (J. Schmidt), in the bladder (Jacubasch, Krawer, Perski, Marchand), and in the ureteral wall (Holzappel).

Metastases in the central nervous system are also frequently seen to occur most often at the level of the left hemisphere, and the most common site is the occipital lobe. They are sometimes found as a single nodule varying in size from a lentil seed to a hen's egg. In other instances they occur in multiple nodules. These secondary growths do not usually have the hemorrhagic aspect of visceral metastases.

In addition to these sites metastases have been occasionally observed in the most diverse organs, as for instance in the stomach, large and small intestines, heart, pericardium, pancreas, spleen, thyroid, suprarenal capsules, diaphragm, bone and subcutaneous cellular tissues.

#### DIAGNOSIS

The diagnosis of chorio-epithelioma is often beset with great difficulties. One should always suspect it when profuse hemorrhage follows a hydatid mole that has been thoroughly removed. To be certain of this, one must employ the procedure advocated by the writer, some years ago; that is, in every case of hydatid molar pregnancy, to perform a hysterotomy, so that the hand may be employed to remove all the vesicles. Another inestimable value of this procedure consists in enabling the operator thoroughly to palpate every portion of the inner wall of the uterus for any suspicious nodule, or extra thinning of the wall, at any one area. In this manner the growth may often be detected in its very earliest stages, as was done by the writer in 2 cases, in his series, and by Eden in one case. For there can be no question, judging from a close scrutiny of the reported cases, that chorio-epithelioma was not infrequently present while

the hydatid mole was still in the uterus. It is safe to place in this category most of the cases of hydatid molar pregnancy, in which the bleeding persisted, or recurred shortly after the uterus was emptied. The case reported by Jellinghaus, already referred to, in the writer's opinion, belongs to this class. If this assumption be correct, then the advice given by Jellinghaus and others, to subject every woman who has had a hydatid mole, to a curettage, every two or three weeks, to determine whether she is developing a chorio-epithelioma, would obviously be unnecessary, to say nothing of the dangers such a procedure would involve. H. Williamson (16) makes the suggestion that the Abderhalden test be made, every few weeks, in every woman who has a hydatid mole, so as to determine the earliest development of chorio-epithelioma. But it must also be borne in mind that in a few cases, a period of amenorrhea intervenes between the removal or expulsion of a hydatid mole, and the first symptoms of the presence of a growth. In Eden's case a period of two months and in Cataruni's case 3 months elapsed. No explanation has been offered for this paradoxical phenomenon. In Eden's case, the growth was evidently present at the time of the hydatid mole, as when he emptied the uterus he detected a small nodule on palpation and thought it was a fibroid nodule.

When the growth follows shortly after labor at full term, the cervical canal is usually patulous. Then it may be feasible to palpate the interior of the uterus with the finger or fingers. The detection of an elevated, fairly hard, nodule with an excavation in the center is almost pathognomonic. The appearance of the characteristic bluish red papules on the vagina or in the vulva, confirms the diagnosis. When the cervix is not patulous, other means have to be employed, which will receive attention later.

The greatest difficulties are encountered when the growth follows an early miscarriage, for in these instances one can never be certain that the persistent bleeding may not be due to placental or decidual residue, even though the curettage may have been done by an expert. In such a contingency, one must have recourse to a microscopic examination which, unfortunately, even by the expert, may not be conclusive, or may even be misleading. Several cases are recorded in the literature in which the microscopic examination by a pathologist of repute and ability, proved to be inconclusive or erroneous. The writer has already referred to an instance of his own, in which a most capable pathologist made an error in diagnosis. When we stop to consider the nature of the condition, we can readily understand how a microscopic examination may be attended with failure. Unless the curette scrapes away some of the deeper tissues, the pathologist has no means of determining whether he is dealing with a new-growth or with normal placental tissue. He can only determine this, if the microscope shows invasion of the deeper structures, for that is the only distinguishing feature between normal chorionic tissue and chorio-epithelioma. To add to the difficulties, a curettage done so as to bring away some of the deeper tissues is not free from danger. It is prone to set free particles of the growth, which may gain entrance into the venous circulation and then bring about rapid and extensive metastases. A close scrutiny of the cases in the literature reveals the fact that the

most rapidly fatal cases were those that were subjected to several curettages before a diagnosis was reached and a hysterectomy performed.

Hitschmann and Cristofolletti lay great stress upon the dangers attendant upon a curettage in chorio-epithelioma. They studied 300 cases in the German literature, and made a comparison between the cases subjected to a curettage and those that were not. In the former, they found that metastases were very much more extensive and rapid than in the latter. They found, also, that the fatal, non-operative cases, had fewer metastases than those subjected to hysterectomy, which terminated in death at an early date. Thus demonstrating that any manipulations of the affected tissues are likely to cause extensive metastases. In studying the reports of the cases in the literature, one cannot fail to observe how much better the results were, when the radical operation had not been preceded by two or three or more curettages, as obtained in many of the cases. The unusually excellent results obtained by the writer, in his series, 8 recoveries in 9 cases, cannot well be explained by the mere assumption that the cases were all of the semi-benign variety. That would be a fortuitous occurrence, not to be paralleled by a series of a similar number of cases, in the literature. It is more within reason to attribute them to the circumstance that the diagnosis was made at an early stage of the disease, than that in every instance the growth was of the non-malignant type.

The only fatality in the series occurred in the case that was subjected to two curettages, the pathological report of the first being misleading, although a tentative diagnosis, on the clinical evidences, had already been made by the writer. In spite of all these considerations, instances will arise where recourse will have to be taken to a diagnostic curettage. The clinical evidence may not be conclusive, it may justify only a suspicion, and one would under these conditions naturally hesitate to remove the uterus in a young woman, without having incontrovertible evidence of the presence of the disease. But if any aid in diagnosis is to be sought from the material obtained by a curettage, one must make sure that the curette has brought away some of the deeper structures, as already has been stated. Occasionally, in a doubtful case, especially in a young woman, one might adopt the method employed by the writer in a case recently.

The patient, aged 26 years, had had a miscarriage of twins, at about the third month, 6 weeks before. She was curetted in a metropolitan hospital on the same day. She continued bleeding, at times quite profusely. The uterus was but slightly enlarged, she was now again curetted, the pathologist reported that the tissues were suspicious of chorio-epithelioma, but he could not be certain of the diagnosis as there was no myometrium in the material. The bleeding recurred in a few days. Not wishing to subject the patient to another curettage, the writer did a vaginal hysterotomy and also anteverted the uterus through an anterior vaginal incision. In this way he was able to palpate and inspect with the naked eye both the inner and outer walls of the uterus. No growth or suspicious area was detected. The wound, in the uterus, was sutured, the organ was replaced in the pelvic cavity and a suture applied to the vaginal wound. The patient has been under observation for over 3 months; she has been perfectly well and menstruation has been normal.

The growth may be situated entirely in the uterine wall or projecting toward the peritoneal surface, and has no connection whatever with the endometrium,

as in a case reported by H. Meyer (17) and another by Nagy (18). Hence the necessity of exploring both surfaces of the uterus.

#### PROGNOSIS

There is no form of malignant new-growth, in which the prognosis varies so widely as in chorio-epithelioma. If the diagnosis has been made early, and the uterus has not been subjected to much manipulation, as is occasioned by several curettages, the prognosis is fairly good. Different from other malignant growths the outcome may be good, even in the face of extensive metastases. Several cases are on record, in which there were evidences of metastases in the vagina and lungs, and the patients recovered with and without operation. A remarkable instance of this kind is a case reported by J. C. Rockafellow (19) in which, after removal of the uterus, large growths recurred in the labia, at intervals of a few weeks. As soon as the growths, sometimes the size of a kidney, were excised they would spring up again like mushrooms, in a week or so. On the fourth recurrence, the patient's general condition was so poor that it did not seem worth while to make any further attempts at removal. To the surprise of every one, in a few weeks, the growths spontaneously began to shrink and in a few weeks more, had practically disappeared, leaving a mere hard ridge at their site. The patient began to improve and in a short time regained good health and remained so as long as she was under observation, which was a period of over two years.

Von Fleischman (20), Hormann (21), Hitschmann and Cristofolletti (*loc. cit.*), each report similar cases. In Hitschmann and Cristofolletti's case, the operation was given up on account of the extent of the tumor, which involved the vagina and bladder, and extended far and wide, in the pelvis. The patient improved rapidly after the operation, and a month later there were no signs of the tumor of the uterus, and the pelvic structures seemed to be free. The patient was in perfect health, seven years later. In one of the writer's cases (Case 4), several small bluish papules appeared on the posterior vaginal wall, after the hysterectomy. These gradually disappeared spontaneously. Neumann (22), Kelly and Teacher (23), Marchand, have each observed spontaneous disappearance of vaginal metastases after removal of the uterus. Risel (24), Eden and Lockyer (25), reported the observation of healed nodules in the lungs, among those still growing, in a case which terminated fatally. Teacher, himself, publishes a similar observation.

Regarding operative results, the statistics published by Teacher (*loc. cit.* p. 590) exhibit the most careful study. In the 189 cases collected, radical operation was performed 100 times. Of the group not operated upon all ended fatally except the case of von Fleischman. Of the 100 cases operated upon, 63 were followed by immediate recoveries, and 37 by death; of the 37 deaths, 12 occurred within a few days, evidently from shock and loss of blood. In the remaining 25 there was no marked improvement, or interval of good health after the operation. "Out of the 63 recoveries, 32 were reported well six months or more after the operation, and out of this number 24 remained well for more than a year, and of these again, 13 were reported well more than two years after the operation.

Among the fatal cases, it was remarkable that in 5 only, did the disease recur after a longer interval than six months, and the longest interval between operation and death was one year. Death after a longer interval has since been reported." Teacher goes on to say: "Still, one is justified in the conclusion that, if the patient survives more than six months without signs of recurrence, the probability of recovery being permanent is considerable; after one year, it is very great, while cases in which two years have elapsed may be regarded as absolute recoveries."

Teacher draws attention to the striking fact that 42 of the cases, with a percentage of recovery of 78, followed hydatid mole. He adds, "Possibly a considerable number of these should not have been described as chorio-epithelioma malignum."

Briquel reported 114 cases with 72 operative recoveries and 42 deaths. Of the 181 cases collected by Pollosson and Violet, there were 126 operative recoveries and 17 deaths from operation. The difference in the operative recoveries, in the two series, could well be explained by the difference in the periods in which they were performed, the one period extending from 1885 to 1903, the other from 1903 to 1912.

Briquel analyzed this series, in reference to the operative results, following the different kinds of pregnancy. In 21 cases following labor at term, there were 12 (57 per cent) recoveries, in 34 cases following miscarriage, there were 20 (58.5 per cent) recoveries, in 54 cases following hydatid mole, there were 37 (68.5 per cent) recoveries, in 3 cases following tubal gestation there was 1 (33.3 per cent) recovery.

The writer is inclined to agree with Pollosson and Violet, that the better results obtained in cases following hydatid mole are probably due to the circumstances that the cases are watched more closely, and the diagnosis, in consequence, is made at an earlier stage.

Before taking up the treatment of chorio-epithelioma, it may be well to devote a short time to the consideration of the treatment of hydatid mole in view of the close connection between the two conditions. This close relationship between hydatid mole and chorio-epithelioma was first established by Marchand in 1895. The frequency with which hydatid mole is followed by chorio-epithelioma has been variously stated by different writers. Bumm in his textbook placed it at 15 per cent. Palmer Findley (26) in a collection of 210 cases found it to be 16 per cent. On the other hand, in 20 cases observed at the Kiel Klinik, only two were followed by chorio-epithelioma. Kehrner (27) followed up the history of 50 cases of hydatid mole and did not meet with a single instance of this complication. The writer, during a period of four years prior to 1911, had observed 8 cases of hydatid mole, 3 of these were attended or followed by chorio-epithelioma. Senarclens (quoted by Pollosson and Violet) was enabled in the Canton of Vaud to observe for a long period of time, 42 out of 49 cases; 35 or 72 per cent were definitely cured by the expulsion or removal of the hydatid mole, 7 or 14 per cent underwent immediate cure, but the remote results were unknown. Three only, or 6 per cent, died from chorio-epithelioma. It is obvious that statistics, such

as these, furnish a more reliable basis as to the relationship between the two conditions than do those coming from hospitals or operators. But granting even that the higher percentage expresses more closely the actual relationship, it would scarcely warrant the attitude of some authorities, that all cases of hydatid mole should, at once, be subjected to a panhysterectomy. When a hydatid mole occurs in a woman over 40 years of age, as not infrequently is the case, it may be the safer course to resort, at once, to hysterectomy, rather than wait for the development of chorio-epithelioma. But it occurs almost as often in young women, ranging from 18 to 25 years, in whom an unnecessary sacrifice of the generative organs would be most reprehensible. Hence, in women, let us say, under 40 years of age, the course advocated by the writer, in a paper (28) read before the New York Obstetric Society, May, 1911, ought to be followed. This, as has already been described above, consists in performing a vaginal anterior hysterotomy, for the double purpose of making certain of removing all vesicles, and of making a thorough exploration, with the hand, of the entire inner walls of the uterus. The woman should then be carefully observed for a long period, and on the occurrence of profuse bleeding, a diagnosis of chorio-epithelioma would be justified.

The treatment of chorio-epithelioma, once the diagnosis has been made, resolves itself into an immediate panhysterectomy, for, as we have already shown, we have no means of determining whether the individual case be a highly malignant one, or one that might undergo spontaneous cure. The latter contingency is so unusual that for all practical purposes it must be left out of consideration.

When the growth is discovered while emptying the uterus of a hydatid molar pregnancy, the natural thing to do would be to complete the operation through the vaginal route. The same would apply when, in a doubtful case, an exploration of the inner and outer walls of the uterus would be made through a vaginal incision. In most all other instances, the abdominal route probably is to be preferred, for it embraces less traumatism and consequently less danger of causing metastases.

Hitschmann and Cristofolletti lay strong emphasis upon the selection of the abdominal route for this very reason, and also because they deem it advisable to excise the deep pelvic veins, as is done in puerperal thrombophlebitis. They assert that the pelvic veins are frequently filled with extensions from the growth. Hence, the necessity of this excision. Should this even be the case, it is doubtful whether the procedure is called for, inasmuch as these venous extensions have a tendency to disappear spontaneously by clotting of the blood, depriving the tumor masses of their source of nourishment. Vaginal nodules, if present, should be excised and, if they occur subsequently, the same procedure might be necessary, although they also have a tendency to disappear spontaneously. Different from carcinoma, the lymphatic vessels and glands are seldom involved, and there is no indication for doing anything so radical as the Wertheim operation. One should not defer doing the operation, in the face of the most unpromising local conditions, for extensive infiltrations are usually due to venous involvement which, as we have seen, has a tendency to disappear spontaneously

after removal of the uterus. Even when there are signs of metastases in the lungs, hysterectomy should not be denied, if the patient be in a condition to withstand the shock of the operation, for there are several cases on record, in which the lung symptoms have disappeared, after the original growth had been removed.

Radium has been employed in a few instances (29), but with only temporary benefit.

*Case 1 (30).* Mrs. E. R., a patient of Dr. Altman, was seen by me January 4, 1907. She was 47 years old, married 26 years, had had eight children, the last seven years ago; one miscarriage 16 years ago. She enjoyed good health, and menstruation had been normal until the present illness. Her last regular menstruation occurred September 27, 1906. On November 10, when she was 17 days overdue, a bloody flow occurred, resembling in amount and duration her usual menses. But the blood did not cease entirely. She continued staining and 12 days before I saw her she had a profuse flow lasting one day, and passed several large clots. She had no abdominal pain until the day of my visit, when she referred it to the lower part of the abdomen and stated that it was moderately severe. Three weeks before, while mounting a flight of stairs she felt a severe fluttering in the cardiac region, and suffered from shortness of breath. She has suffered, more or less, from similar symptoms since then and complained of great weakness. Swelling of the feet and legs was noted about this time and the swelling has kept on increasing until now. She had taken to bed the day before on account of general debility and the unwieldy size of the feet and legs. She was extremely anemic, her breathing rapid and shallow, pulse rapid and rather bounding. There was a soft blowing murmur accompanying the first sound and the cardiac impulse was diffuse; cardiac dullness considerably increased. The abdomen was occupied by a spherical smooth tumor, reaching to the upper border of the umbilicus. On bimanual examination, the cervix was found soft and moderately patulous and passed into the abdominal tumor. The breast nipples were surrounded by a dark areola but no colostrum was found. The urine contained a large quantity of albumin and numerous granular and hyaline casts. The diagnosis was made of a probable pregnancy of an abnormal type, or a fibroid growth undergoing sarcomatous degeneration. The advice was given to have the patient enter Mount Sinai Hospital, and under anesthesia to explore the uterine cavity. This was done on January 9, and although only a few days elapsed since I had examined the patient, the uterine tumor had markedly increased in size, so that now it reached midway between the umbilicus and the ensiform cartilage. As soon as I could introduce the index finger into the uterine cavity, after dilating the cervix, and it encountered a soft, mushy material, I recognized I had to deal with a hydatidiform degeneration of the chorion. I rapidly emptied the uterus of its contents, making certain that all the hydatid material was removed. The patient made a surprisingly good recovery. Her cardiac and pulmonary symptoms disappeared within a few days. The albumin in the urine rapidly disappeared and the casts gradually grew less.

There was a slight bloody flow for four or five days, then a mucopurulent flow for four or five days longer, and after that there was no discharge of any kind. The patient returned home and was gradually gaining in weight and improving in color, when on February 1, she was suddenly seized with a profuse uterine hemorrhage. I advised the attending physician to pack the vagina and to make immediate arrangements for the patient to be readmitted to the hospital. I saw her two days later. She was considerably exsanguinated. In replacing the vaginal gauze there was a very severe hemorrhage. I rapidly stuffed some gauze into the uterine cavity and repacked the vagina tightly. From the clinical history and on finding an enlarged, hard uterus, with closed cervix, I diagnosed chorio-epithelioma malignum. On the day following, February 4, I performed an abdominal panhysterectomy, not deeming it safe to wait to curette and submit the scrapings to a microscopic examination. She made an uneventful recovery from the operation. Patient well up to the present.

*Pathological report* by Herbert L. Celler, Assistant Pathologist, Mount Sinai Hospital. (Specimen consists of uterus and adnexa.) The uterus is very pale. Length of body 2.5 centimeters, width just below fundus 11 centimeters, length of cervix 4 centimeters. The organ is very firm, the serosa smooth. There is a slight lateral laceration on the right side of the posterior lip of the cervix. The walls of the fundus measure 3 centimeters in thickness at the widest part. The muscular tissue is intersected by numerous bands of connective tissue that coalesce near the mucus to form a more continuous broad band. The mucus lining both the body and cervix is smooth, except at the internal os where there is a slight swelling and congestion, and at the point of entrance of the Fallopian tube. At the latter site there is a bean-shaped mass 1.5 centimeters in length, projecting into the lumen of the organ. This tumor is mottled in color, red and white, soft and friable. The underlying muscular tissue is softer than that of the remainder of the uterus, and is also friable. The hemorrhagic areas are, however, confined to the tumor itself, and are not found in the underlying muscular tissue. The right ovary is normal in size. The left ovary contains two large cysts, one about 1.5, the other about 2 centimeters in diameter. Both Fallopian tubes are negative.

Microscopically, the tumor consists of both syncytial masses and Langhans cells. The former are arranged in plaques and in bands, in some places forming a fine meshed reticulum. The spaces thus formed are frequently filled with red blood corpuscles, or contain one or more cells of the syncytial or Langhans type. The former are irregularly shaped, deeply staining, the outlines of the cell not always clearly defined. The nuclei are also irregular, and stain with great intensity. Frequently these cells contain two, three, or four nuclei. The Langhans cells stain faintly, and have a sharply defined outline. The nuclei are round or oval, and vesicular. The greater part of the tumor is composed of the above syncytial masses, but at one point there is a large mass of Langhans cells. Large hemorrhages are scattered throughout the tumor. At some points the syncytial cells lie close to the walls of blood-vessels or lymph spaces, an occasional cell being present within the lumen itself. The tumor infiltrates the musculature of the uterus for about one-third of its thickness. Scattered between the syncytial masses are numerous leucocytes, while surrounding the entire area of tumor tissue there is a marked round-celled infiltration. Between the tumor and the lumen of the uterus there is a thin band of necrotic tissue enclosing leucocytes and the remains of a few uterine glands. The walls of the blood-vessels of the uterus have undergone hyaline degeneration.

Both ovaries show a number of corpora lutea in which the lutein cells are proliferated. These bodies are small with the exception of one that lies in the midst of the dense tissue of the atrophic ovary. Here there is very marked proliferation of the lutein cells, many of which contain large granules of yellowish pigment. At the periphery of the corpus there are rather numerous distended blood-vessels with thin walls. There are no evidences of organization present.

Diagnosis kindly verified by Dr. F. S. Mandelbaum, Pathologist.

*Case 2* (31). G. H. admitted from the dispensary service into Mount Sinai Hospital. She was 47 years of age, married 28 years, had nine children, last child eight years ago, two miscarriages, last one nine years ago. Menses had always been regular moderate in amount, lasting from three to five days and not attended with pain. Seven days before her admission into the hospital she began to bleed. She was then two weeks overdue. The bleeding persisted and at times was quite profuse. She looked rather old for the age given and was moderately anemic. Her general condition, otherwise, was good. On bimanual examination, the uterus was found reaching to within two fingerbreadths of the umbilicus and was rather hard to the touch. There was a bluish discoloration of the vagina, and milk could be expressed from the nipples. Dr. F. Krug confirmed the diagnosis of hydatid mole, which was made in my service in the dispensary. He curetted the patient himself, removing a large quantity of hydatid material. The patient made a good recovery and was discharged March 3, with the instruction to return if uterine bleeding recurred. At the time of her discharge the uterus was nearly normal in size. On March 28, she returned to the

hospital with the statement that soon after she left the hospital the bleeding recurred, and it has gradually been growing more profuse. The uterus was now found to be considerably enlarged, corresponding in size to the gravid organ at about the sixth week. A diagnosis of chorio-epithelioma was made and on March 30 the uterus removed by me, *per vaginam*.

April 8. The patient made an uneventful recovery and is sitting up out of bed. She was well two years later, when last heard from.

Report on specimen by Dr. F. S. Mandlebaum, Pathologist to Mount Sinai Hospital. The specimen consists of uterus and adnexa. The uterus is enlarged, 11 x 9.5 x 5 centimeters. The wall measures 17-30 millimeters in thickness. Occupying the posterior wall and extending downward from the fundus for a distance of 48 millimeters, there is a growth which fills up and slightly distends the uterine cavity. On either side the growth extends to the openings of the Fallopian tubes, elevating the mucous membrane and causing it to slope downward to the opening. The tumor is sessile. Its edges are overhanging, except at the upper half. The surface of the tumor is irregular and ulcerated, and microscopic section shows it to be chorio-epithelioma malignum.

Case 3. Mrs. C. G., admitted to Mount Sinai Hospital, May 1, 1912. She was 36 years old; married 17 years; VI-para, last child  $4\frac{1}{2}$  years ago; no miscarriages except this present one; menses established at 14 years, four-weekly type, duration 2 days. Her last menses occurred 14 weeks ago. Two weeks ago uterine bleeding set in which has persisted up to the present; uterus the size of the gravid organ at 12 weeks.

May 2. Uterus emptied by Dr. F. Krug. The cervix was patulous, admitting the insertion of the index finger with which the membranes were ruptured. A small fetus and placenta was secured with placental forceps, and the uterine mucosa thoroughly curetted with the sharp curette.

May 14. Discharged from the hospital. The following note was made at this time: Uterus moderately enlarged and lying in retroversion.

June 5. The patient was readmitted, stating that for 2 weeks she felt well and then began to bleed very profusely, which was 10 days ago. The bleeding has persisted until now. The patient is quite anemic. Local findings about the same as when discharged 3 weeks ago. The uterine bleeding is very profuse, necessitating packing of the vagina.

In view of the history and the certainty that none of the ovular products were left behind by Dr. Krug, a diagnosis of chorio-epithelioma was made.

June 6. Abdominal panhysterectomy was performed by the writer. The patient made an uneventful recovery. A year later was in good health.

*Macroscopic report*, June 6, 1912. The specimen consists of the uterus, the left adnexa complete; and the right tube. The right tube in its distal half is thickened and tortuous; its abdominal ostium is closed by adhesions. The left tube in its distal half is also thickened and tortuous, not quite so much so as that of the other side. The abdominal ostium is patent. The left ovary is somewhat enlarged, studded with small cysts up to size of a pea. The uterus is slightly enlarged. In the left cornu is a small lobulated, firm tumor fixed to the uterine wall and invading it for a short distance. The mass measures 2 x 4 centimeters and is grayish in color. The rest of the uterus and cervix is apparently normal.

*Microscopic diagnosis*. Chorio-epithelioma.

Case 4. Hydatid mole. Chorio-epithelioma. Double ovarian cysts. Hysterectomy. Postpartum eclampsia. Recovery.

Mrs. S. C. was referred to me by her physician, Dr. J. S. Diamond. She was eighteen years old, married fifteen months. Menses at fourteen years, four-weekly type. Duration three to four days. Amount moderate, not with any pain.

Six months after marriage went two weeks overdue and then began to bleed. Was supposed to have a miscarriage and was curetted. Her menses were regular after this for four months and then ceased for two months, when she began to bleed irregularly; at first scantily and later rather profusely. When she consulted me the bleeding had been going on for about two months.

She was very pale, sallow, and looked very ill. The uterus reached up to the umbilicus

and was rather tense. The cervix was closed. Behind the uterus lay two irregularly shaped cystic masses each about the size of a closed fist. The urine contained a large amount of albumin and numerous hyaline and granular casts. There was no edema. The diagnosis was made of an abnormal pregnancy with double ovarian cysts.

Operation, November 22. Finding, on attempting to empty the uterus, that it contained a hydatid mole and as both ovaries were cystic, I decided to perform a panhysterectomy, which I did, removing the cervix also. The operation offered no unusual difficulties and consumed about an hour. The patient withstood it very well. At 5 o'clock the next morning, twelve hours after the operation, the patient was seized with a severe convulsion, lasting about ten minutes. This was followed by coma of twenty minutes. From this hour until 11 a. m. she had, in all, seven convulsions, each followed by coma of longer or shorter duration. The urine was very scanty, loaded with albumin and showed very numerous granular and hyaline casts. Temperature had risen to  $104^{\circ}$  and pulse 180, very small and soft.

The patient was subjected to the usual treatment for eclampsia; in addition, phlebotomy was done, about sixteen ounces of blood withdrawn, and colon irrigations with saline solution were given. She showed signs of improvement toward the evening of the same day when the temperature fell to normal although the pulse still remained very high (140 to 160). From this on improvement was steady and on November 30, eight days after the operation, the urine showed merely a trace of albumin.

The removed uterus on microscopic examination showed quite an area of chorio-epithelioma on the posterior wall near the fundus. The ovaries were cystic throughout and showed little or no stroma. There was no excess of lutein cells. December 12. Patient discharged from the hospital as cured.

January 15, 1911. She was again referred to me by her physician on account of bleeding from the vagina. I found a small vascular growth in the center of the vaginal scar and dotted over the posterior wall of the vagina were small flat papules about the size of a split pea and of a bluish-red color. I suspected a recurrence and had her readmitted to the hospital. On January 19, I excised the growth with the Pacquelin cautery and also cauterized the papules on the vaginal wall. The removed growth showed no evidence of chorio-epithelioma, consisting only of connective tissue with blood cells. Patient left the hospital January 25.

May 8. Patient called at my request. She was in good health, her color had become good, she gained in weight. There had been no recurrence of the bleeding. The vaginal wound was healed and the entire vault was smooth and normal in appearance. Two years later when last heard from was well.

*Macroscopic report*, November 22, 1910. The specimen consists of uterus measuring 13 centimeters from internal os to fundus. The wall measures 2.5 centimeters in thickness. The uterine mucosa is covered throughout by necrotic, velvety tissue which is thrown up in places into markedly rugous and almost papillomatous masses. On section, sinuses of uterus are markedly enlarged, the cross section of the muscularis having a fenestrated appearance. Both ovaries are enlarged into irregular ovoid, orange-sized, completely cystic masses with straw-colored, mucin-like contents, some of them containing blood.

*Microscopic diagnosis.* (a) Chorio-epithelioma. (b) Polycystic degeneration of both ovaries. No marked proliferation of lutein cells. (c) Hydatidiform mole.

*Case 5.* Chorio-epithelioma. Abdominal panhysterectomy. Recovery.

Mrs. C. B. was admitted to Mount Sinai Hospital on March 17, 1911. She was 36 years old, married at 18 years, 7 children, the youngest child being 23 months old. Menses at 14 years of age, irregular, three to four-week period up to two years ago; since then, menorrhagia of 2 to 10 weeks at a time. The last regular period was 12 weeks ago; bleeding since. For past 2 years she has had slight pain in the lower abdomen, associated with backache and slight leucorrhea.

Vaginal examination showed the uterus to be uniformly enlarged to size of 10 weeks' pregnancy; fairly soft; the adnexa normal; and the presence of a good-sized rectocele and cystocele.

March 21. The patient had a rather profuse hemorrhage from the uterus. She became pulseless and required very active stimulation. Hemoglobin 64 per cent. Pan-hysterectomy by Dr. Krug.

The specimen consists of a fibroid uterus about the size of a 3 months' pregnancy. In the cavity there was a shaggy mass attached by a pedicle to the fundus, resembling very much a piece of placenta, which might be a necrotic submucous fibroid.

April 17. Patient was discharged in good condition.

*Macroscopic report*, March 21, 1911. The specimen consists of the uterus which is enlarged. The uterus shows marked hypertrophy of the wall which measures 3 centimeters. Near the fundus on the anterior wall is an area, covered by soft granular and fungoid tissue which causes a thickening of from 1 to 4 millimeters in the endometrium. Besides this is tissue which appears to be amnion and chorion.

*Microscopic diagnosis*. Chorio-epithelioma.

*Case 6*. A. H. was admitted to the Mount Sinai Hospital on June 12, 1911. She was 33 years old, married 12 years, five children, last child 21 months ago, doubtful miscarriage 3 months ago. Menses at 14 years, four-weekly type, duration 7 days. Three months before, when menses were due, she merely stained. A month later stained again. At the recurrence of the next menses, she flowed very profusely and suffered with pain in the right iliac region. She was then admitted to the Lying-In Hospital, where she was curetted for a miscarriage. The flow persisted after the curettage and so did the pain. On admission the patient was found to be moderately anemic. The uterus was about of normal size and the adnexa were apparently normal.

In view of the history of the case, chorio-epithelioma was suspected. Not desiring to subject the patient to another curettage, it was decided to explore the uterus visually by an anterior colpotomy, and if necessary by an anterior hysterotomy.

*Operation*, June 15. A transverse incision was made in the anterior vaginal fornix; and the uterus delivered through it. In the right cornu was seen a small vascular tumor the size of a filbert, and presenting the characteristic bluish discoloration of a chorio-epitheliomatous growth. The operation was completed by extirpating the uterus and adnexa through the vagina. The patient made a rapid recovery and was discharged on July 1. She was under observation for two years and remained perfectly well.

*Macroscopic report*, June 15, 1911. The specimen consists of the uterus with both tubes and ovaries. The uterus measures 7.5 x 5 x 3 centimeters. It is the normal multiparous shape. The cervix shows a shallow old laceration to the right. The wall of the uterus is 1.5 to 2.2 centimeters in thickness. A papilliferous mass is situated at the fundus in the neighborhood of the right horn. Its base is 1.7 centimeters wide and 2.2 centimeters long (from above downward), and the mass projects about 5 centimeters beyond the surface of the mucosa. The tumor is fairly firm and is pinkish brown in color. Both ovaries are of about normal size and cystic (old corpus luteum cysts). No recent corpus luteum of any prominence is visible.

*Microscopic diagnosis*. Chorio-epithelioma.

*Case 7*. Chorio-epithelioma. Septicemia-streptococcemia. Hysterectomy. Death. Mrs. L. L., 31 years of age, married 5 years, had 2 children, one three and a half years ago and the second four months ago. She was seen in consultation by me March 18, 1910, for persistent uterine bleeding. Her medical attendant, an intelligent practitioner, informed me that he had delivered the patient at term with instruments four months before. The patient went through a normal puerperium, but the flow of blood in small quantities persisted for three weeks. It then ceased for three weeks when it recurred and continued off and on in slight amounts, until two weeks before, when rather a sharp hemorrhage took place. He then curetted her, removing apparently several fragments of placental tissue. This put a stop to the bleeding for some days when it recurred again slightly with rather a free flow now and then. On the night previous she had a profuse flow of blood. I found a strong, healthy looking woman inclined to obesity, with moderate pallor of the lips. She was nursing, and the infant seemed to be thriving satisfactorily. On bimanual examina-

tion I found the uterus enlarged to the size of the gravid organ at about six weeks. The cervix was patulous, admitting the index finger readily, which on exploring the uterine cavity detected a sessile growth on the anterior surface of the uterus, near the left horn, corresponding in size to about a fifty-cent silver coin, raised above the surface about one-fourth of an inch, and presenting on its surface a shallow depression. There was no marked hardness of the growth. I made the diagnosis of a probable chorio-epithelioma, and stated that I would be more certain of the diagnosis had not a curettage been done a short time before. I argued that a placental residue, the other alternative in diagnosis, would not present a crater-like excavation on its surface. But here entered the element of doubt. Could not the excavation have been produced artificially by the curette? I advised, therefore, her entrance into Mount Sinai Hospital where the growth could be removed with the curette and subjected to microscopic examination. I curetted her that afternoon in the hospital without anesthesia in the presence of Dr. F. S. Mandlebaum, the pathologist of the hospital. The curette removed so much tissue that looked like ordinary placental tissue that both he and I thought that it was an ordinary case of bleeding from placental remains. The temperature, rectal, before curettage was 100.8°F., pulse 108. March 19, temperature, 99 to 100.4°F., pulse, 100 to 108. March 20, temperature, 99.6 to 100°F., pulse, 96 to 100, no bleeding.

Report from the pathologist stated that removed tissue showed nothing more than normal decidual structures. Being anxious to have the patient return to her nursing infant as soon as possible I had given orders to have her transported home in the ambulance. On the following morning, March 21, just as the patient was being gotten ready to be sent home, she had a moderate flow of blood. She was taken into the examining room and the interior of the uterus gone over lightly with a curette on the supposition that a small fragment of tissue might have been left behind. The curette did not bring away enough tissue to account for the bleeding. She had scarcely been returned to her bed when she had a severe hemorrhage and she was at once brought back to the examining room and the uterus packed tightly with iodoform gauze. I now felt that we had, in all probability to do with a malignant growth, notwithstanding the report from the laboratory, and requested that a further examination be made of the tissue removed that morning. Four p. m., temperature, 102°F., pulse, 136. Assuming that the fever was due to the uterine packing, the house surgeon removed two pieces of gauze from the vagina, under the belief that on so doing he had removed all the gauze that had been employed in packing. March 22, 4 and 8 a. m., temperature, 99.4°F., pulse, 116. Four p. m., temperature suddenly rose to 104°F., pulse, 120; 8 p. m., temperature, 105.6°F., pulse, 134. I had seen the patient in the morning when her temperature was normal and concluded that the temperature of the evening before was due to retention due to the uterine packing which was relieved by removal of the gauze. In the evening her condition was reported to me and I immediately visited the patient. On specular examination, I found that the house surgeon had removed only the vaginal packing and that the uterine gauze was still *in situ*. I removed it and irrigated the uterus with alcohol 50 per cent. March 23, 8 a. m., temperature, 105.6°F., pulse, 140; vomited once. Blood culture taken. Decided to remove the uterus as soon as consent could be obtained. Eight p. m., temperature 103.8°F., pulse, 148. Hysterectomy. Owing to the patient taking the anesthesia poorly and to the great abundance of fat in the abdominal wall and in the subperitoneal tissue of the pelvis, it was not feasible to carry out ligation of the pelvic veins. Patient withstood the operation very well. March 24, 8 a. m., twelve hours after operation, temperature, 103.2°F., pulse, 140.

March 24, 4 p. m., chill, temperature, 106.4°F., pulse, 140 to 180. March 25, 4 a. m., patient died.

Notes from the pathological laboratory. March 18, 1910. Specimen of retained placenta received. Decidua with markedly atypical cells, some very large with giant nuclei. Diagnosis is in doubt, but it is suspicious of malignant change.

March 23, 1910. Uterus received for examination. Organ is moderately enlarged, and musculature is soft and flabby. Uterus measures 9 centimeters; wall considerably thick-

ened, 18 x 25 millimeters. Mucosa shows evidence of curettement. In the body anteriorly is a lenticular avid tumor occupying the site of the mucosa, and the tissues immediately underneath infiltrate the muscularis for about 1 to 2 centimeters. On section this area measures  $3\frac{1}{2}$  x 2 centimeters and is composed of soft, hemorrhagic, necrotic tissue. The microscopic sections of the uterine tumor show the so-called atypical variety (Marchand) of chorion epithelioma. In the superficial zone there is extensive necrosis, hemorrhage, and conglomerate masses composed of atypical, acidophile syncytium and cells of the Langhans type; in the deeper layers, syncytial masses and chorionic wandering cells of bizarre shape penetrate the muscle for a considerable distance and are also found free in the blood sinuses. Diagnosis: chorion epithelioma.

Autopsy performed on March 25, 1910, at 2 p. m., by Dr. A. E. Cohn. Case of chorio-epithelioma with pulmonary metastases. Body of an adult adipose female. Panniculus adiposus well developed. Operative incision in the median line above the symphysis pubis, about 15 centimeters long.

The lungs are both voluminous, pinkish gray in color. Adhesions between lobes and between lung and pleurae. Scattered through right lung, but more especially projecting along borders, are small tumor masses varying in diameter from 3 to 10 millimeters. On cut section they project sharply above the surface of the lung and are sharply circumscribed, and have a "port wine" and a somewhat reticulated appearance. The reticulum is grayish. The dependent portions of the lung are congested. There is no consolidation; no tubercles; no metastases. The bronchi are congested; the pulmonary arteries are normal. The left lung shows adhesions similar to the right, except that there is no fibrinous exudate on surface. There are about twelve metastases of the shape and size described.

The heart is normal in size with marked fatty overgrowth. The pericardium is normal. The right auricle is somewhat dilated, but not the right ventricle. There are marked chiri over the coronary sinus, the muscle is flabby and pale. The tricuspid valve admits two fingers, the edges of the valve are retracted, thickened, but show no recent lesion. The aorta shows fairly marked atheroma, the posterior much less than the anterior. Foramen ovale closed.

The liver shows slight parenchymatous and fatty degeneration, otherwise normal.

A slight perisplenitis is present but diffuent. The lymphatic structures of the spleen are not easily made out.

The kidneys show marked parenchymatous degeneration.

Floor of the pelvis is clean. There is some bluish discoloration along the line of suture. The vesical veins show no abnormality. The inferior vena cava in its lower half shows no thrombosis.

*Microscopic examination.* There are metastases in the lung. The tumor mass itself is composed of large blood sinuses together with necrotic areas into which there has been hemorrhage. Scattered through the tumor, but especially at the periphery there are groups of cells characterized by irregularity in size and shape. Nuclei for the most part are large and vary in their amount of chromatin; some of them are almost vesicular and others show a dense network. The cell bodies, where they can be observed, are irregular in shape and finely granular. A number of cells show karyorrhexis. These cells are for the most part isolated, having only a slight tendency to form groups. A number are vacuolated. The diagnosis of chorio-epithelioma is made.

*Case 8.* R. W., aged 50. Married 26 years; ten children; last child eight years ago. Three miscarriages, last seven years ago. Patient consulted me May, 1911. She stated that her menses for the past year had been irregular, occurring from four to eight weeks. A month ago, after a period of amenorrhea of eight weeks she began to bleed. The bleeding persisted with varying intensity up to the time of her seeing me. I found the uterus enlarged, had the sign of a gravid organ of about 12 weeks. It had a soft doughy feel. A diagnosis of hydatid mole was made, and the patient given a card of admission to Har Moriah Hospital.

May 15, 1911, operation. Vaginal hysterectomy. Uterus emptied with the hand of about

a quart of characteristic vesicles. Interior of uterus palpated. A suspicious nodule was felt in the posterior wall. Operation completed by doing a vaginal panhysterectomy. Microscopic examination by the pathologist of the hospital confirmed diagnosis of chorio-epithelioma, which was also confirmed by Dr. L. S. Mandlebaum, pathologist to Mount Sinai Hospital. Patient in good condition up to the present, seven years after the operation.

*Case 9.* Mrs. J. S. admitted to the Mount Sinai Hospital on November 3, 1915. She was 44 years old, married for 26 years, had seven children, one dead, youngest child six years old; all pregnancies full-term, and normal delivery; one miscarriage. Menses began at 14 years, regular every month, duration from four to five days. Up to six weeks ago patient had amenorrhea for past five months. During this time she commenced to bleed, and this has continued steadily and progressively up to the present time, much blood being lost.

Physical examination revealed the following: The abdomen, was soft, relaxed, tympanitic. There was a mass present, reaching almost to the umbilicus, hard and smooth in consistency, conforming to shape of a gravid uterus of four months' advancement. The mucous membrane of the vaginal canal was of a violet hue. The uterus was large, ante-flexed conforming to size of pregnant uterus of almost four months. Adnexa were not felt. Cervix not patulous, direction down and forward.

November 5, 1915. Hysterotomy and emptying of uterus for hydatidiform mole performed by Dr. S. Wiener. November 15, 1915. Uterus well involuted. Hysterotomy wound, slight gaping at one point. November 16, 1915. Patient discharged in good condition.

*Pathological report,* November 10, 1915. Tissue from uterus-hydatid mole.

November 17, 1917. Patient readmitted. Diagnosis chorio-epithelioma. Vaginal flow daily for four months. (Through courtesy of Dr. Joseph Brettauer).

Vaginal examination disclosed a moderate cystoretocoele; cervix hard and nodular. Uterus anterior, slightly enlarged. Fundus globular and hard. Both fornices clear. Uterine bleeding. Sound determines small smooth sound nodules on left lateral and anterior walls. Slight tear in perineum. Uterus slightly enlarged.

November 19, 1917. Exploratory curettage by Dr. Lindeman. November 21, 1917. Cervix gauze removed. Patient's condition good. Extra systoles more frequent, otherwise no signs of cardiac lesions.

November 22, 1917. Vaginal hysterectomy for chorio-epithelioma by Dr. Lindeman.

Specimen. Uterus slightly enlarged. Normal tubes and ovary. On opening the uterus there was present in the fundus a small (2 centimeters) friable, pedunculated tumor, dark brown in cross-section and on surface, extending only a short distance into uterine tissue. November 19, 1917. Curettings show evidences of malignant tumor suspicious of chorio-epithelioma. November 22, 1917, uterus and adnexa show chorio-epithelioma.

December 3, 1917. Patient discharged from hospital in good general condition.

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## THE RELATIVE INFREQUENCY OF CANCER OF THE UTERUS IN WOMEN OF THE HEBREW RACE<sup>1</sup>

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In a short paper on the "Etiology of Cancer of the Pelvic Organs," read before the New York Obstetrical Society (1), January 9, 1906, the writer drew attention to an observation he had made during a service of fifteen years in The Mount Sinai Hospital Dispensary. Although the service was a large one, visited by the class of women that ordinarily should furnish a fairly large number of cases of cancer of the uterus, he was struck with the rarity with which that disease was encountered. Being cognizant of the almost universal opinion that laceration of the cervix was a potent cause of cancer of that organ, he paid especial attention to all cases with reference to that point. Every case presenting the slightest suspicion of malignancy was subjected to a thorough examination and kept under observation for a long period afterwards to determine the correctness of the microscopic report. It may, therefore, be fair to assume that very few cases escaped detection. This assumption receives further confirmation from the fact, to which the writer has frequently drawn attention, that it is very rare indeed that one meets with cancer of the cervix, especially of the vaginal portion, the most common variety, in which the diagnosis is not unmistakable on palpation and inspection with the naked eye. In other words, when cancer of the cervix gives rise to symptoms, it is almost always so far advanced that the diagnosis is positive without the aid of the microscope. The suspicious cases, as a rule, with very few exceptions, prove not to be such. That, at least, has been the writer's experience and that of a good many other gynecologists with whom he has spoken.

The data, therefore, regarding this point, which the writer collected from his Dispensary service from 1893 to 1906, a period of thirteen years, may be regarded as approximately accurate. There were during this period 19,800 new patients. Among these there were 1995, or about 10 per cent, with marked laceration of the cervix. There were in all 18 cases of cancer of the cervix. Here comes the strikingly interesting point: Roughly speaking, 95 per cent of the patients were of the Hebrew religion and natives of Russia, Austria, and Poland. Still of the 18 cases of cancer of the cervix only 9 cases, 50 per cent, occurred among this class of patients, while the other 9 cases were met with among the non-Jewish women, who constituted only 5 per cent of the patients. Consequently the incidence of cancer of the cervix was twenty times greater in the non-Jewish than in the Jewish women. When one stops to consider that of the total number of the Jewish women 1995 had badly lacerated cervixes, that they were all immigrants

<sup>1</sup> Reprinted by courtesy of Paul B. Hoeber, Inc., from Contributions to Medical and Biological Research, dedicated to Sir William Osler, in honor of his seventieth birthday, July 12, 1919, by his pupils and co-workers.

who, according to Max Schüller, (2) show a much greater predisposition to cancer than do the natives, and that they were living in the worst possible hygienic surroundings, amidst the greatest squalor and privation, such as obtain in the lower East Side of the Metropolis, it is truly remarkable that so few cases of cancer of the cervix were detected amongst them.

My associate and friend, Dr. I. C. Rubin, made a painstaking investigation of the cases in all of the gynecological services in the Mount Sinai Dispensary from December, 1909, to December, 1918—a period of nine years.

The total number of new cases examined approximated 30,000. Total number of positive cases of cancer of the cervix was 20. Total number of suspected but not established cases of cancer of the cervix was 50. This included hypertrophied, eroded, ulcerated, and bleeding cervixes in which subsequent control failed to establish cancer, or in which curettage, partial excision of the cervix for diagnostic purposes and hysterectomy did not result in a positive finding of cancer. The proportion of cases of cancer of the cervix in this material was therefore 20 in 30,000, or 1 in 1500 cases. Of these 20 cases 13 were in Jewish women and 7 in non-Jewish women. The 7 non-Jewish women were either Americans or of the Slavic immigrant class.

The general proportion of non-Jewish to Jewish women at the Dispensary during this period was about one in 15,<sup>2</sup> consequently the actual incidence of cancer of the cervix in the Jewish patients of the Dispensary was 13 in 28,000, or 1 in 2154 cases. In the non-Jewish women it was 7 to 2000, or 1 in 285, or  $7\frac{1}{2}$  times greater than in the Jewish women.

It is interesting to note the close ratio of the incidence of cancer of the cervix in the Jewish women in the two series, that of 1893–1906 and of 1909–18. In the one it was one in 2089 cases, in the other one in 2154 cases. But the ratio in the non-Jewish women shows a marked difference. In the first series it was one in 111 cases, in the second series it was one in 285 cases.

Dr. Rubin investigated also the records of The Mount Sinai Hospital during the same period. From December, 1911, to December, 1918, there were: Carcinoma of the cervix, 58 cases; of the uterus, 35 cases; of the vagina, 5 cases. The total number of patients admitted to the Gynecological Department during this period was approximately 7000. The total number of adult females admitted to the hospital during the same period was 30,000. As each of these patients was subjected to a thorough and careful physical examination as a matter of routine, and wherever the slightest suspicion existed a special gynecological examination was added by one of the attending gynecologists, it is quite natural that the percentage of cancer of the cervix would be much higher than in the dispensary cases. The difference in the ratio can further be explained by the fact that practically only operative cases are admitted to the gynecological services of the hospital.

But the point that has a special bearing upon our contention is the ratio existing between the non-Jewish and Jewish women. Of the 65 cases of cancer of the cervix 32 were in Jewish and 33 in non-Jewish women. As the same ratio ob-

<sup>2</sup> Based on an actual count for two years of the period.

tains in the hospital<sup>3</sup> as in the dispensary, that is, 1 to 15, the general incidence would be for Jewish women, 32 to 28,000, or 1 in 937 cases; non-Jewish women, 33 to 2,000, or 1 in 61 cases. The incidence therefore is fifteen times greater in the non-Jewish patients than in the Jewish patients treated in the hospital.

*Occurrence of carcinoma in other viscera.* For this purpose the year December, 1917, to December, 1918, was chosen.

Carcinoma of the rectum, 23 cases: Jewish, 21; non-Jewish, 2. In this series there were 9 in females and 14 in males.

Carcinoma of the intestines, 23 cases: 11 in females, 12 in males, 19 Jewish, 4 non-Jewish, of which 3 were females.

Carcinoma of the stomach, 43 cases: 18 females, 25 males, 37 Jewish, 6 non-Jewish, 4 women and 2 men.

Carcinoma of the breast, 17 cases: 6 non-Jewish.

Contrasted with the occurrence of carcinoma in other organs than the uterus, it appears that carcinoma of the cervix is a little more than eight times as infrequent as carcinoma of the rectum; eight times as infrequent as carcinoma of the intestines, exclusive of the rectum; sixteen times as infrequent as carcinoma of the stomach, and about seventeen times as infrequent as carcinoma of the breast.

In other words, there are treated as many cases of carcinoma of the rectum or of the intestines *in one year* at The Mount Sinai Hospital as there are carcinoma of the cervix uteri cases in eight years, and twice as many stomach cancer cases in one year as there are cancer cervix cases in eight years.

This is highly significant in view of the fact based on statistics (references to which occur later) that in the relative frequency of cancer of the individual organs, that of the uterus stands first in the list.

The writer has made a search of the literature and found but very meager references to the subject. What he did find was all confirmatory. After the time the writer made the observations here under discussion he interrogated several colleagues who were likely to come into contact with the same class of patients. They all said that since their attention had been drawn to it, they recalled that their experience corresponded with his own.

A. Theilhaber (3) draws attention to the slight disposition of Jewesses to cancer of the cervix. In 228 cases of fibromyoma 49 (19.1 per cent) were Jewesses; in 133 cases of cancer of the cervix only 1 (0.75 per cent) was a Jewess. He learned that this experience was confirmed by others.

F. Theilhaber (4) states that disease statistics in Germany are not classified according to religion. But such a classification exists in the city of Budapest. In that city the Jews are fairly equally divided among all classes of inhabitants. They show a marked increase of births over the others. He furnishes statistics to demonstrate that the number of childbirths have a bearing upon cancer of the cervix.

Holfmeier and others have published statistics demonstrating a similar ratio between the number of childbirths and the occurrence of cancer of the cervix.

<sup>3</sup> Based on an actual count for two years of the period the same as for the dispensary.

Theilhaber emphasizes the significance of the fact that Jewesses reach an older age than do other Budapest women. Hence their participation in all diseases in which age bears an influence should be greater. He states that the mortality among Jewish children is much less than among other children. This, of course, as a natural consequence advances the age of the Jewish population, so that under the Jewish deaths almost double as many old people are to be found as under the deaths of all the other population.

To quote further from Theilhaber's paper, in the year 1906 there were in all 16,360 deaths in Budapest, among which were 2500 Jews, or 15 per cent; 27 per cent, excluding cancer of the uterus, died of cancer, but only 8.05 per cent died of cancer of the uterus; thus there were only one-third of the number which one would expect from the cancer deaths *in toto*.

Theilhaber quotes from H. Kirschner unpublished data in reference to the city of Munich. In that city from 1876 to 1908 there died 185 Jews from cancer, of these there were 98 women. Seven of these had cancer of the uterus, so forming only 7 per cent of the cancer cases in the Jewish women. The usual ratio of

TABLE 1

NUMBER OF BIRTHS	CANCER OF THE CERVIX	FIBROMYOMA
	<i>per cent</i>	<i>per cent</i>
0	4	39
1	13	19
2	15	13
3-5	33	19
6-8	15	9
9-10	10	1
11-15	10	0

cancer of the uterus is from 25 per cent to 35 per cent of all cases of cancer. That the Jewesses of Munich did not show such relative immunity from cancer of other organs is evidenced by the fact that during the same period 41 died of cancer of the stomach and of the intestines.

Birch-Hirschfeld has asserted that the relative frequency of cancer of the individual organs may be stated according to the following scale: 1, uterus; 2, external skin; 3, mamma; 4, stomach.

A. Theilhaber and S. Greischer (5) furnish further statistics from Munich and Nürnberg (Table 4). It will thus be seen that in Munich the percentage of deaths from cancer of the uterus among Jewesses was but one-fifth of those among the Christians. On the other hand, the percentage of deaths from cancer of the mamma among Jewesses was nearly double as great as that among Christian women.

The writer consequently believes that the fact has been fully established that cancer of the cervix of uterus is much less frequently met with among Jewesses, particularly of those belonging to the poorer classes and hence among the most orthodox, than among the women of the Christian religion.

The fact has also been established that so far as cancer of the other organs is concerned no such immunity exists. On the contrary, if anything, statistics demonstrate that Jewesses are more prone to cancer of the other organs than are their Christian sisters.

The question now arises, to what factor or factors may be attributed the comparative immunity of this particular organ? What is there in their mode of living and habits that stands out prominently as being different from the poorer classes of other religions? No explanation, as far as the writer is aware, has been offered by any of the authors who have written on the subject. We know that

TABLE 2  
*Deaths in Budapest*

YEAR	TOTAL DEATHS	JEWISH DEATHS	TOTAL CANCER DEATHS	JEWISH CANCER DEATHS
1906	16,380	2,500	785	183
1905	16,094	2,623	867	153
1904	15,435	2,614	1,009	192
1903	15,059	2,468	896	188
1902	14,732	2,400	869	167

TABLE 3  
*Deaths from cancer of uterus*

YEAR	TOTAL	JEWESSES	JEWISH CANCER DEATHS
		<i>per cent</i>	<i>per cent</i>
1906	149	12— 8	23.3
1905	142	15—10.5	17
1904	170	13— 7.7	19
1903	150	18—12	20.9
1902	172	10— 5.8	19.1
Total.....	783	68— 8.7	19.5

There is no separation in the above statistics of cancer of the cervix from that of the body, so that many of the cases may have been cancer of the body.

whatever differences there may exist regarding squalor, poverty, and unhygienic surroundings are not in their favor.

The writer himself in the article referred to ventured an explanation. It occurred to him that the only marked difference in their mode of living and habits from that of the women of most all other religions consisted in their strict observance of the Mosaic Law regarding marital relations. Sexual congress is prohibited during menstruation and during seven days following the cessation of the flow. The Mosaic Law<sup>4</sup> commands that the woman count seven unclean days (whether the flow lasts that long or not) and seven clean days before she takes the bath of immersion and marital relations are resumed. If the flow should

<sup>4</sup> Leviticus XV, 19 seq.

persist for more than seven days or return before the count of the seven clean days had elapsed, the count of the seven clean days must begin anew. Thus in cases of menorrhagia or metrorrhagia sexual intercourse might not be permitted for months.

Again after parturition the Mosaic Law<sup>5</sup> enjoins abstinence from the sexual act for a variable period, depending upon whether the birth was of a male or female child. My learned friend Dr. D. de Sola Pool states that these laws are only the starting points for an extended development in actual Jewish life—"one sixth of the whole Talmud is given up to laws of women, including the laws of marriage, divorce, etc., and the laws in which you are especially interested." He further states the official formulation of Jewish law compiled towards the end of the Middle Ages, which is still the authoritative code of traditional law, "demands the counting of fourteen days for a male and twenty-one days for a female child be-

TABLE 4

## Munich, 1907-1909

Christians		<i>per cent</i>
Total number of deaths.....	1326	
Number of deaths from cancer of uterus and mamma.....	501	37.7
Number of deaths from cancer of uterus.....	381	28.7
Number of deaths from cancer of mamma.....	120	9
Jewesses		
Total number of cancer deaths.....	102	23.5
Number of deaths from cancer of uterus.....	7	6.8
Number of deaths from cancer of mamma .....	17	16.7

## Nürnberg, 1907-1909

Jewesses		
Total number of cancer deaths.....	30	
Number of deaths from cancer of uterus and mamma.....	6	20
Number of deaths from cancer of uterus.....	1	3.3
Number of deaths from cancer of mamma.....	5	16.6

fore the woman is permitted to her husband." "There are places where it is the custom not to take the bath of purification after childbirth until forty days after the birth of a son and eighty days after the birth of a daughter. It has become the general rule throughout Israel not to cohabit so long as there is any blood whatsoever, even 'clean blood.' Therefore, if there is any appearance of blood after seven or fourteen days, even though the Biblical law allows cohabitation, it is customary to wait for seven complete days after the disappearance of the last vestige of blood before allowing cohabitation."

It is well known that the poorer classes of non-Jewish women not only do not observe such restrictions, but are in the habit of indulging in cohabitation during the menstrual period and very shortly after parturition.

If there is one thing in which there is a consensus of opinion regarding the etiology of cancer it is that continued irritation, especially under unfavorable

<sup>5</sup> Leviticus XII.

conditions, is a potent causative factor. That sexual irritation under any condition is a predisposing cause is evidenced by the fact, established by all available statistics, that cancer of the cervix is much more common among the married and widowed than among the non-married.

Accepting this proposition, then, it must be granted that cohabitation during the menstrual period or immediately thereafter, when the uterus is still in a high degree of congestion, must increase markedly the harmful effect of the irritation of the sexual act at ordinary times. It must be borne in mind, in consequence of their adherence to the Mosaic Code, the orthodox Jewish woman is subjected to this irritation of the sexual act for practically only two weeks out of four. And that in cases of metrorrhagia (having to count seven clean days) the sexual act may not be allowed for months at a time. That sexual intercourse after parturition before the bloody discharge has ceased must cause hyperirritation must also be granted.

The writer is fully aware that the theory he offers does not permit of substantiation by scientific experimentation. But in our present ignorance of the cause of cancer a collection of carefully sifted clinical data regarding an organ ordinarily prone to cancer may prove of some value in the solution of the problem of cancer etiology.

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## THE HIRAM N. VINEBERG FELLOWSHIP IN GYNECOLOGY

In January, 1936, the Board of Trustees of The Mount Sinai Hospital accepted the offer of Dr. I. C. Rubin to establish the Dr. Hiram N. Vineberg Fellowship in Gynecology.

This Fellowship has been awarded to the following:

Dr. Udall J. Salmon.....	1936-1938
Dr. Emanuel Klempner.....	1939
Dr. A. M. Davids.....	1940
Dr. Jack Squire.....	1941
Dr. Joseph Novak.....	1942
Dr. S. Sugár.....	1943

The scientific contributions made by these Fellows during their tenure of the Fellowship are as follows:

- Frank, R. T. and Salmon, U. J.: Extraction of Gonadotropic Factors from the Blood. Improved Technic. *Proc. Soc. Exper. Biol. & Med.* 34: 363, 1936.
- Salmon, U. J. and Frank, R. T.: Quantitative Relation Between Follicle Stimulating and Luteinizing Effects in Castrate and Menopause Urine. *Proc. Soc. Exper. Biol. & Med.* 34: 463, 1936.
- Frank, R. T. and Salmon, U. J.: Time Factor Relationship of Follicle Stimulating and Luteinization in the Immature Rat. *Proc. Soc. Exper. Biol. & Med.* 35: 493, 1937.
- Salmon, U. J. and Frank, R. T.: Effect of Emmenin on Gonadotropic Hormone Excretion in Castrates and Spontaneous Menopause. *Endocrinology*, 21: 476, 1937.
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THE WILLIAM HENRY WELCH LECTURES  
I. RENAL PHYSIOLOGY BETWEEN TWO WARS\*

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It was in the summer of 1920, while recovering from an appendectomy, that A. N. Richards conceived the idea of so arranging a frog's kidney that he could examine the glomeruli directly under a microscope. It may seem that there is no great amount of inventive ingenuity in this procedure, yet it constitutes a milestone in the history of renal physiology. And behind it was what one might call a flowing tide of ideological necessity: a tide on which Richards and his coworker Schmidt were but flotsam and jetsam, destined to be cast up on the shores of science in a new experiment. The waves of ideological necessity which bear men to their experimental fates are frequently as interesting as the experiments which they produce, and are worthy, in this case at least, of a close examination.

Richards, while giving a course in experimental pharmacology at the College of Physicians and Surgeons between 1903 and 1908, had become interested in the isolated mammalian heart as a means of studying the action of drugs upon this organ. With John Howland, he had also been struggling with liver function, particularly those problems concerning detoxification, and it had seemed to him that an adequate perfusion technique, one better than any hitherto described, might unlock the answers to many circulatory and hepatic problems. He had formulated a plan for an ideal perfusion pump not involving any metal, when he moved to Pennsylvania as Professor of Pharmacology in 1910. In the summer of 1911, Cecil K. Drinker came to work with him and they constructed a machine which successfully perfused the brain of a cat for nearly two hours. Just as they were beginning to perfuse a kidney with some success, as measured by an encouraging trickle of urine, Drinker had to leave Philadelphia to start his internship at the Peter Bent Brigham Hospital.

Oscar H. Plant took Drinker's place and during the next year or so he and Richards completed a series of experiments in which they showed that urine formation was related primarily to the blood pressure in, rather than the blood flow through, the kidney, thus offering a rebuttal to an argument that stemmed from Heidenhain, who had found that the rate of excretion of certain dyes is roughly proportional to the blood flow<sup>1</sup>, and generally independent of the

\* Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, January 5, 1943.

<sup>1</sup> The relative importance of blood flow and blood pressure in determining the function of the kidneys had been a matter of controversy for nearly fifty years. The modern demonstration that the excretion of many dyes and other substances (phenol red, diodrast, various hippuric acid derivatives, etc.) is proportional to blood flow and *not* to the rate of water excretion (which is what the earlier workers generally meant by "urine formation") reveals that there was some basis of truth for Heidenhain's contention.

blood pressure. More noteworthy, however, was their observation that adrenalin in proper doses caused the kidney to swell, even though at the same time it caused a rise in the perfusion pressure required to maintain a constant blood flow.

This paradox was difficult to explain in conventional terms of vasomotor action, which required vasodilatation, and therefore a decrease in perfusion pressure, as the basis for the expansion of an organ; but Richards and Plant soon resolved the difficulty by suggesting that the locus of action of the adrenalin was the *efferent* glomerular arterioles, constriction of which would cause swelling of the glomeruli and anterior portions of the vascular bed at the same time that it caused an increase in perfusion resistance, and therefore in overall perfusion pressure.

Then in April of 1917 came the war, and these experiments, except for a preliminary note, went unpublished for five years. In August of 1917 Richards went to England as consultant to the British Medical Research Committee. In 1917-18 his investigations were confined to some experiments with Dale on the paradoxical action of histamine on isolated organs, in contrast to organs *in situ*, experiments planned in an effort to gain some light on the genesis of traumatic shock. In the interval before he went across the Channel to take charge of the Physiological Laboratory of the Chemical Warfare Service at Chaumont in 1918, he also met Arthur Cushny, and the two became close friends.

Cushny had obtained his M.D. degree at Aberdeen in 1892, and had come as Professor of Pharmacology to the University of Michigan at the age of twenty-seven. In 1905 he had returned to the Chair of Materia Medica and Pharmacology at the University of London, and in 1918 had gone as Professor of Pharmacology to Edinburgh, a Chair which he held until his death in 1926.

His monograph on "The Secretion of Urine," which appeared in 1917, has been described as the first coherent theory of the mode of action of the kidney which accorded with modern knowledge of physical chemistry, even as his textbook on "Pharmacology and Therapeutics and the Action of Drugs" was the first comprehensive textbook on this subject. Dixon, writing of Cushny at the time of his death in 1926 remarked, "The present generation has little understanding of the sacrifices which men like Cushny made to pursue their ideal. Nowadays, men fitted for research can obtain an ample wage, but in those days (1900-1926) £100 per annum was affluence; and it is small wonder that the few like Cushny, who for a time survived, leave a mark on history which is ineradicable."

When Cushny came into the field, the physiology of the kidney was made up, as he said, of "a wrangle of two great views of its activity." In a wrangle, the man who can talk the most usually comes out on top, even though his position may be insecure. It was Cushny's wish to reduce the loose talk and confounded theories then enveloping the kidney to a minimum, while expanding in some small measure the body of solid fact. With a determination that amounted

almost to cruelty to theorists, he relegated their confused papers, which he said were more marked for their length than depth, to the library where they could be allowed to continue to collect dust as was their proper fate, while he sought out and organized a few tangible facts which he thought everyone could and would believe.

Cushny came into renal physiology by way of the intestinal tract. Back in 1897-98 at Ann Arbor he and George Wallace had been studying the action of saline cathartics; they had found that sulfates and phosphates are not easily absorbed through the intestinal epithelium and had ascribed the catharsis induced by these salts to the osmotic pressure thereby set up in the intestinal contents. It was but a short step to argue that sulfate and phosphate diuresis is similarly the result of the failure of these salts to be reabsorbed by the renal tubule. A simple notion, but against the background of the last decade of the nineteenth century, a profound one. When Hans Meyer spoke of sulfate diuresis as "renal catharsis," he summed up the new idea in catch phrase.

In subsequent years Cushny came under the influence of Starling, and indeed Starling was the editor of the series of "Monographs on Physiology" of which Cushny's work ("The Secretion of Urine") was the second volume. It is interesting to note in passing that the first of this series had been Gaskell's "Involuntary Nervous System," while the later members included Sherrington's "Physiology of Reflex Action," Keith Lucas' "Conduction of the Nervous Impulse," Dale's "The Physiological Basis of the Action of Drugs," Fletcher's "Nature of Muscular Movement," Mott's "The Cerebral Mechanisms of Speech," and Lovett Evans' "Tissue Respiration." A more distinguished coterie of monographs has certainly never been published.

But to return to the editor, Starling, or rather to the author of the second of Starling's series, Cushny, it was certainly the one who influenced the other towards the acceptance of a belief in a simple physical process of glomerular filtration which owes its origin to the hydrostatic pressure of the blood, and owes nothing to the vital nature of the glomerular capillaries except some degree of impermeability to the plasma proteins.

In 1917 Colonel Starling was in Egypt fighting World War I, and it was there that he read the manuscript of Cushny's monograph. That monograph seems cumbersome now, because from the beginning the author has to fight his way through a maze of elective theories—apart from laboratory data of the first order there were no facts, not even the central idea of glomerular filtration could be set forth as a demonstrated fact. Consequently Cushny endeavored to prepare the way for the student, lest he become wholly lost in the vapors of contradictory speculation, by setting forth what he aptly called his "Modern Theory."

Accepting the premise that urine formation begins in the gomerulus with ultrafiltration, at the expense of the hydrostatic pressure of the blood, of a filtrate containing all the plasma constituents other than the molecularly gigantic proteins, Cushny sought to preserve simplicity by positing that it was the sole function of the renal tubules to reabsorb from this filtrate a fluid of

constant and optimal composition, a perfected Locke's solution or protein-free plasma, in such optimal quantities as are required to maintain the optimal composition of the plasma. What was left behind in the tubules passes on into the bladder as urine. "The formation of the glomerular filtrate," he said, "is due to a blind physical force, the absorption in the tubules is equally independent of any discrimination, for the fluid absorbed is always the same, whatever the needs of the organism at the moment."

In retrospect, we can question if the reabsorption of a fluid of "optimal composition" and containing several dozen substances, the conservation of which is advantageous to the organism, is indeed a simplification over the alternative hypothesis that the renal tubules reabsorb these substances independently, in accordance with as yet unidentified factors determining the reabsorption of each substance more or less separately.<sup>2</sup> The past twenty years have shown that the latter explanation is actually the case: tubular reabsorption of each constituent does in fact proceed more or less independently of the reabsorption of other constituents; so perhaps our philosophical quibble about "simplicity" is only hindsight. Nevertheless, one thinks that Cushny would have been happy to have had each valuable constituent of the glomerular filtrate reabsorbed independently were it not that this explanation seemed to entail a terrifying multiplicity of operations on the part of the tubule cells, and this multiplicity of function was just what Cushny was determined to expel from renal physiology. And for a very good reason: multiplicity of function is apt to become elastic, even elective, until running riot it escapes from all descriptive rules and becomes a rule into itself. It ends in vitalism, wherein every cell operates in mysterious ways and under its own wilful determination to achieve some far-off, if not divine, event. Vitalism was still a living issue in Cushny's day, it had scarcely been expelled from nerve-muscle physiology,<sup>3</sup> while many explanations of renal activity were essentially vitalistic in nature. Cushny had no desire to aid and abet this enemy of deterministic science. As he says of his monograph, "If it serves as an advance post from which others may issue against the remaining ramparts of vitalism its purpose will be attained."

But such are the difficulties inherent in ideas, and in the words which we use to designate them, that on page 53 of this same monograph Cushny says that the reabsorption by the tubules of an optimal quantity of fluid of an optimal composition "depends on the *vital* activity of the epithelium." Reducing vital activity to these two by four dimensions and depriving it of the prerogatives of qualitative and quantitative discrimination seems to be a matter of confining the vital force by dialectic chains.

<sup>2</sup> Water, Na, K, Ca,  $\text{PO}_4$ , Cl,  $\text{HCO}_3$ , glucose, various amino-acids, vitamins, hormones . . . not all these substances have been studied in detail but the available information is sufficient to indicate that the list is a large one. For recent studies on the reabsorption of water, Na and Cl see Shannon (26, 27), of K see Winkler and Smith (37), of  $\text{PO}_4$  see Harrison and Harrison (11), of  $\text{SO}_4$  see Goudsmit and Keith (10), of glucose see Shannon, Farber and Troast (28), of amino-acids see Doty (7), of vitamin C see Friedman, Sherry and Ralli (8), of hemoglobin see Monke and Yuile (19).

<sup>3</sup> Sherrington's monograph on the "Integration of the Nervous System" had not yet been written.

It was, however, not the multiplicity of tubular reabsorptive processes that worried Cushny, but the presumed process of tubular secretion, in which the tubular cells were supposed to abstract from the blood, this, that and the other constituent and deposit them in the tubular urine. If we posit the tubular secretion of three diverse substances we seem to require a three-fold discrimination on the part of the tubule cells, and why stop at three? Why not say ten, fifty or a hundred diverse substances are excreted by the tubules, which know just what to pick up out of the blood, just when to abstract it, and just how much to excrete?

Heidenhain had posited the existence of a process of secretion not only in the tubules but in the glomeruli themselves, which he supposed secreted water and salts, and from his time on whenever an investigator found himself in difficulty with an experimental fact he had too frequently been prone to invoke tubular secretion to explain it. It is a case of simple arithmetic: if you have three explanations, glomerular filtration, tubular reabsorption, and tubular secretion, you can dispose of the most horrendous unknown by the judicious application of two out of the three available solutions. In the first quarter of the century renal physiology was the sporting ground for this kind of dialectic, and it was Cushny's determination to drive the deterministically offensive one, tubular secretion, out of the field. His position was that when the adherents of tubular secretion came across with some believable and convincing evidence they would be admitted to respectability; until then they were *persona non grata*.

It was in this milieu of the Cushny renal renaissance that Richards came home from the War in December 1918. Getting together with Plant, they wrote up their experiments on the perfused kidney, guided by Cushny's analysis of the evidence on renal theory. Then in the Spring of 1920 Richards was invited to give a Harvey Lecture and immediately thereafter he came down with an acute appendix. In the ensuing forced vacation he pored over his perfusion experiments and the adrenalin paradox, some reprints of Krogh's papers on capillaries, and Cushny's monograph. Filled with admiration for Krogh's technique of direct observation of the capillaries in the tongue, foot and mesentery of the frog, he conceived that if he could see the glomeruli at work he might obtain a confirmation of the Richards-Plant adrenalin paradox, and thus in his Harvey Lecture be able to present a demonstrated fact rather than an hypothesis. When he got back to the laboratory in the early Autumn he suggested the experiment to Carl F. Schmidt, then an instructor in his department.

No sooner said than done, and what Richards and Schmidt saw under the microscope is now familiar to every student of renal physiology. On the ventral surface of the kidney an occasional glomerulus could be discerned, the capsule distended with fluid, the blood cells moving in a thick stream through the active capillary loops. The most cursory examination showed that the circulation in some glomeruli was much more active than the circulation in others; and indeed in any one glomerulus the number of active capillaries showed considerable variability, a single capillary passing in the course of a short time from a state of activity, wherein the blood flow was abundant, to one of inactivity

in which the motion of the cells was slow or wholly arrested. Thus Richards and Schmidt came to speak of the "intermittency of glomerular activity," and to conclude that in the normal kidney not all glomeruli are active at any one time.

These observations on the intermittency of glomerular activity in the frog have been repeatedly confirmed, but their implications for the mammalian kidney are not yet clear after a period of twenty years, and we may set the question of intermittency aside for a moment while considering other features of the experiment. It was all pretty exciting stuff. I can remember hearing about it in Boston, where I had just come to Walter Cannon's department as a National Research Council Fellow. In fact, I heard so much about it in Boston that for a considerable period I labored under the impression that the experiment had been done at Harvard. The basis for this confusion was probably the circumstance that Joseph Wearn, who had been an assistant resident at the Brigham Hospital in 1919 to 1921, went to Philadelphia in the summer of 1921 to join Richards as instructor in pharmacology. Wearn probably sent back such glowing reports on the frog kidney, and they were received with such interest, that out on Longwood Avenue the invention seemed to be indigenous.

It was Wearn who now undertook with Richards the application of the Chambers' microdissection technique to the examination of the composition of the glomerular fluid, Schmidt having left Philadelphia for China. The microdissection technique was not all planned out in advance, like a well-fought military campaign. Richards simply showed Wearn how to look at a frog kidney, asked him to perfect himself in the technique, and to go on looking at it; but to come to him if he had any ideas. Meanwhile, Richards was drifting around and drifted into a meeting of anatomists in which Robert Chambers was demonstrating his microdissecting needle. It occurred to Richards, and he talked it over with Wearn one night after dinner, that Chambers' technique might enable them to test their explanation of the adrenalin paradox by applying the drug directly to the afferent and efferent arteriole. Wearn went farther, and suggested that they puncture the glomerular capsule, withdraw the capsular fluid and analyze it. Fired with enthusiasm, they tackled this difficult task and finally succeeded.

The full development of the micro-study of the kidney was a long and arduous affair. Fifteen years elapsed before the definitive publications on the composition of glomerular and tubular urine made their appearance from the Philadelphia laboratories. Arthur Walker joined the staff in 1925, and in later years James Bordley, John Barnwell, R. C. Bradley, Phyllis Bott, and B. B. Westfall. The painstaking elaboration of capillary analytical methods applicable to the minute amounts of fluid collected from a glomerular capsule or a renal tubule is in itself an achievement of no small importance. The first paper by Wearn and Richards recorded that the glomerular fluid is essentially free of protein, but contains sugar even when simultaneous bladder urine is sugar-free. Cnshny was delighted with that result. Subsequent papers developed the quantitative

technique until it could be said that in the capsule fluid, or glomerular urine, the glucose, phosphate, urea, uric acid, phenol red and creatinine concentration is just what would be expected in a protein-free ultrafiltrate.<sup>4</sup> Thus the doctrine of glomerular filtration now rests upon a bed of fact.<sup>5</sup>

The study of tubular function had necessarily to be carried out in a more or less random fashion, puncturing a tubule wherever it presented itself in a vulnerable position and blocking it fore or aft with a droplet of mercury; but by this method it was shown that glucose and phosphate are reabsorbed in the proximal tubule, and chloride in the distal tubule; that it is in the distal tubule that the urine is acidified, and in the distal tubule that the urine is made hypotonic to the blood.

Thus there was substantiated the filtration-reabsorption theory, in its broader terms, as it had been formulated in the most elementary sense by Ludwig in 1844, and accepted with slight modification by Cushny in his "Modern Theory" in 1917.

But there remained the vexing question of tubular secretion: did it actually exist, and if so, what part did it play in the formation of urine?

It might seem that the micro-study technique would quickly answer this question, but the answer was not so easy to attain. Recognizing that highly varying quantities of water are reabsorbed from the glomerular filtrate as it passes down the tubules, one cannot say from the degree to which any particular constituent is concentrated over and above the original glomerular filtrate (or, if you wish, the plasma) whether that degree of concentration is due to tubular secretion or merely to the reabsorption of water. Indeed, even if tubular secretion is dismissed *a priori*, one cannot say whether various urinary constituents have been in part reabsorbed. What is required in order to answer the question is a *standard of reference for water reabsorption*, some substance which can be demonstrated to be neither reabsorbed nor secreted by the tubules; then from the degree of concentration of this standard of reference one can

<sup>4</sup> A summary of this work is given by Richards in his Croonian Lecture (23), in his second Harvey Lecture (21) of which he justly made Arthur Walker co-author, and in the Carpenter Lecture (22). Detailed papers appear in the American Journal of Physiology, 118: 111-173, 1937.

Walker, Bott, Oliver and MacDowell (36) have recently extended the micro-technique to rats and guinea pigs and shown that glomerular fluid, entirely or nearly free of protein, contains reducing substances and creatinine in concentrations similar to those existing in plasma rates. All the reducing substances (glucose) and at least two-thirds of the fluid are reabsorbed in the proximal tubule, where some chloride reabsorption also occurs, the proximal tubular urine remaining isotonic with plasma.

Bott and Richards (5) have shown that the glomerular membranes are coarse enough to permit the passage of particles of 20 A. in diameter, with some passage of particles of 50 A. (mol. wgt. of roughly 58,000).

<sup>5</sup> Including the recent work on the rat and guinea pig, the demonstration of glomerular filtration in cold blooded animals may be considered an inadequate basis for accepting the simple, physical nature of the process in all animals. An almost equally cogent demonstration that the principle applies to dog and man is, however, available in the study of simultaneous clearances, described later in this paper.

determine the extent of reabsorption of water, and hence whether any other substance has been reabsorbed or secreted. But before that standard of reference was to come, the question of tubular secretion was destined to be answered in the affirmative by E. K. Marshall, Jr.

Trained as a chemist before he went into medicine at Hopkins, Marshall's development of the urease method in 1912 had led him, in collaboration with D. M. Davis, to make observations on the distribution of urea throughout various organs in the body. One day Marshall and Davis happened upon two dogs which had been adrenalectomized by Samuel Crowe, and discovered the marked retention of urea which follows adrenalectomy.<sup>6</sup> This led them into a study of the influence of the adrenals on the kidneys and, prior to the War, in collaboration with A. C. Kolls, Marshall had started a series of experiments designed to study the influence of the nerves on renal function, experiments which were set aside when he took up work on war gases in New Haven in the summer of 1917. Here, however, he read Cushny's monograph and came to feel that some of the results which he and Kolls had obtained were incompatible with a simple filtration-reabsorption theory.

In the Fall of 1917 Marshall went to the Chemical Warfare Station at American University in Washington, D. C., and it was here that I met him the first week in January of 1918. I had originally been assigned to a battalion of Liquid Flame Throwers in the Engineers, but through the good graces of Col. Wilder D. Bancroft I was transferred to American University where I worked with Marshall and Lynch on mustard gas.

The war over, and gas warfare no longer of interest, Marshall returned to Hopkins where with Kolls he published their pre-war experiments, with additions, in 1919. By this time Marshall had become intrigued with the ambiguities and mysteries of tubular function, and in 1923 he and J. L. Vickers published a paper entitled "The Mechanism of the Elimination of Phenolsulphonephthalein by the Kidney, a Proof of Secretion by the Convoluted Tubules." This proof consisted of the demonstration that after intravenous injection of phenolsulphonephthalein the dye accumulates in the cortex of the non-secreting kidney at a time when the blood pressure is too low to permit the formation of significant quantities of filtrate; and, second, that the dye is to a great extent absorbed or combined with plasma protein, only a small fraction being filtrable; consequently, the quantity of free and filtrable dye in the plasma is inadequate on any acceptable estimation of the rate of filtration to account for the total quantity excreted in a given time. In retrospect, the arguments in this paper are unassailable and must, I think, be taken as the first demonstration of tubular secretion in the mammalian kidney.<sup>7</sup>

These experiments were followed in the next year by a paper by Marshall and Crane, adding new and equally convincing evidence, in the demonstration

<sup>6</sup> This retention is now known to be a consequence of circulatory-renal failure.

<sup>7</sup> See 16 and 14. If the evidence of this paper was unconvincing to many, no doubt of tubular excretion could remain after Marshall's (12) demonstration in 1931 that 70 per cent of the phenol red in the renal arterial blood is removed in one passage through the kidney, despite the fact that only 25 per cent is filtrable.

that as the plasma level of phenol red is raised the rate of excretion ultimately levels off and approaches a constant, maximal value; this result is incompatible with a theory of exclusive filtration, but is explicable in terms of filtration plus tubular secretion, the secretory cells becoming saturated at higher plasma levels. At this same time Mayers adduced equally good evidence for the secretion of uric acid by the chicken kidney: the quantity excreted at a given plasma level being inconceivably greater than could be excreted by filtration alone, under any plausible assumption concerning renal blood flow and filtration rate.

Here, in effect, the matter stayed for several years. Proponents of the Cushny theory remained skeptical of Marshall's phenol red experiments, while the proponents of tubular secretion became skeptical of their opponents' reason. Then in 1926, Marshall, browsing through comparative anatomy, discovered that a number of fishes had been described which possessed purely tubular kidneys. This fact, of course, immediately evoked Marshall's interest in fish urine. Unfortunately, aglomerular fishes were rather rare,<sup>8</sup> but we happened to have one species, the goosfish, at Salisbury Cove where I had been working in the summer, and Marshall joined us there in the summer of 1926 to study goosfish urine.

Work on the aglomerular fishes had been undertaken independently by J. G. Edwards in the Naples' laboratory, and within a short time it was clear that this purely tubular kidney, which does not even possess a significant arterial blood supply but is perfused entirely by venous blood from the renal portal vein and at a pressure which is probably below the osmotic pressure of the plasma proteins, can excrete all the ordinary urinary constituents: water, creatine, urea, uric acid, magnesium, sulfate, potassium and chloride: and, among foreign substances, iodide, nitrate, thiosulfate, sulfoeyanide, indigo-carmin, neutral red and phenol red. About the only three important things it would not excrete were ferroeyanide, protein and glucose. Marshall recalls this negative discovery as the high point of his experiences in renal physiology, and it was from this point that Jolliffe and I took off in our later attempts to find a carbohydrate which could serve as a standard of reference for water reabsorption in the tubules, a search which led, after a false start with ferroeyanide and xylose, to the use of inulin.

So, by 1930, the question of tubular excretion was answered in the affirmative. But, as Richards said in the discussion when Marshall read a paper at Woods Hole on the aglomerular fish, "At last he has found an animal that fits in with his theory!" To prove tubular excretion in an aglomerular fish or the tubular excretion of phenol red in the dog, was only to prove the *possibility* of tubular excretion in other animals; the demonstration really answered no questions so far as the frog or man was concerned, for conceivably the situation might be

<sup>8</sup> The aglomerular fish kidney represents an evolutionary adaptation to a salt-water habitat where, because of the hypertonicity of the environment, water conservation is imperative. The known list of aglomerular fishes represents six families and at least a dozen genera, and includes the familiar toadfish, midshipman, goosfish, batfish, sea horse, and pipefish, while many others have greatly reduced glomerular function. A discussion of the evolution of the vertebrate kidney is given in the Porter Lectures (31) and a discussion of various aspects of this problem is available in other papers (13, 15, 29).

different in every species, and certainly it would differ for different substances. Further progress required that a standard of reference by which water reabsorption in the tubules, or to use the corollary of this statement, the rate of glomerular filtration, could be measured.

The renal physiology which I have reviewed up to this point has been rather more qualitative than quantitative. For the quantitative approach we must transfer to another field of investigation, and cut back again to the early part of the century. Strauss in 1903 and Widal and Javal in 1904, had introduced the determination of blood urea into clinical medicine for diagnostic purposes. But this datum by itself was untrustworthy, since it was contingent not only upon the capacity of the kidney to excrete urea but also upon the protein intake. Gréhan in 1904 had tried to use the urine/blood concentration ratio as an index of functional capacity, but this was worse than the blood urea alone, since the concentration of urea in the urine varied with the urine flow, which was of course not only an uncontrolled, but clinically an uncontrollable variable.

Ambard and Weill in 1912 attempted to relate the rate of urea excretion to the blood urea in a dynamic sense, but it so happens that because of back-diffusion the excretion of urea at varying urine flows is a rather complex affair, and Ambard and Weill ended up with an equation that contained two square root radicles.<sup>9</sup> When used empirically, a square root radicle is a mathematician's device to squeeze a correlation out of data in which a simple correlation is not present, and Ambard and Weill's resort to this device did not serve appreciably to clarify renal physiology.

In 1914 Franklin C. McLean, who had been professor of Pharmacology at Oregon, had been studying the blood sugar<sup>10</sup> in diabetes and was on his way to Breslau to work with Minkowski when the abrupt declaration of war stopped him on the Atlantic Seaboard. He went instead to the Rockefeller Institute as a resident. Mathematically minded, McLean had already been intrigued by Ambard's formula, and now he sought to rearrange it into a more rational urea excretion index.<sup>11</sup> Conceiving that this index should be constant in the

<sup>9</sup> Ambard and Weill's equation was

$$\frac{Ur}{\sqrt{\frac{D}{Wgt.}} \sqrt{C}}$$

where  $Ur$  = blood urea in gm. per liter

$D$  = rate of excretion of urea in gm. per 24 hours

$C$  = Urea concentration on the urine in gm. per liter

$K$  = constant

<sup>10</sup> McLean had made the first blood sugar determinations in this country, using the Bertrand method wherein the copper reduced by something like 100 cc. of plasma was filtered out and weighed.

<sup>11</sup> McLean's (17) formula was

$$\frac{\text{gm. urea per 24 hours} \sqrt{\text{gm. urea per liter urine} \times 8.96}}{\text{weight in kg.} \times (\text{gm. urea per liter of blood})^2} = \text{urea excretion index}$$

McLean's reason for making this change was that mathematically the most important factor determining the value of  $K$  in the Ambard and Weill formula is the blood urea, and

diseased as well as the normal kidney, he studied two cases of chronic nephritis over a two months' period, while the patients were kept on a low and a high protein diet. He found that the nephritic kidney responds with increased urea excretion in the face of an elevated blood urea just as does the normal kidney, the mechanism of excretion remaining the same, the only difference between the two being that the nephritic kidney, to use the terms current in the period, shows a greater resistance to the passage of urea. Had McLean said that the capacity to excrete urea relative to the blood concentration is reduced in the diseased kidney, the description would have been essentially modernized. McLean abandoned this study when he was called to China to organize the Peking Union Medical School, and left renal physiology behind him with his chief, Donald D. Van Slyke.

At about this same time Thomas Addis and D. R. Drury demonstrated that the rate of urea excretion divided by the urea content of the blood was fairly constant if the urine flow was maintained at high levels by water diuresis.<sup>12</sup> Addis thought that the administered water increased the excretory capacity for urea by a nervous or humoral mechanism; actually the diuresis itself, by reducing the back-diffusion of urea, appears to be the chief factor in explaining the constancy of the Addis index under these conditions. But the administration of water apart, the constancy of the Addis ratio still had no explanation in renal physiology. The situation was not inaccurately summed up when, at about this time, on addressing the Academy of Medicine, he closed his remarks with an emphatic "All we know *for certain* about the kidney, is that it makes urine."

One of the chief results of Addis' observations was to force the quantitative mode of thinking into experimental renal physiology in this country. Paradoxically, Addis has good-naturedly deplored to me the invasion of the quantitative and experimental method into clinical medicine: "There was a time, not so long ago, when physiology was the handmaid of medicine and you know how disastrous was that bondage. But today there seems to me a danger that medi-

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since only the square root of the rate of excretion of urea and the fourth root of the concentration of urea in the urine are used, moderate impairment of urea excreting capacity might yield a normal value for  $K$ . The use of the factor 8.96 merely served to bring the normal urea excretion index to 100.

<sup>12</sup> Addis and his co-workers (1, 2, 3) found a wide variation in normal subjects when the formula of Ambard and Weill was used, and he substituted the simple formula

$$\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 cc. of blood}} = \text{excretion ratio}$$

What Addis' ratio says is that the excretion of urea per unit time is proportional to the concentration in the blood, and independent of the urine volume. (Neglecting the effects of back-diffusion through the tubules, which are most marked at low urine flows, this is essentially the true relationship.) Since the numerator of Addis' ratio is the urea excreted in one hour's urine, the figure actually represents the urea concentration times the hourly volume and, except for the difference in the time element, the ratio is identical with the maximal urea clearance of Möller, McIntosh and Van Slyke; i.e., the Addis ratio when obtained at high urine flows corresponds to an hourly maximal clearance.

For a detailed study of the effect of urine concentration on the tubular reabsorption of urea in the dog, see Shannon (24), and for a similar study in man, see Chasis and Smith (6).

cine may be sterilized by becoming an appendage of physiology. . . . Young clinicians, dazzled by new experimental methods, are in danger of becoming poor doctors, and they should remember that they are doctors, first, last and all the time." To this I would reply that if the use of quantitative methods and quantitative thinking ends in making poor doctors, it would indeed be tragic, but such need not be the case. I think that quantitatively-minded doctors can be better doctors than qualitatively-minded ones. And I can also retort that my friend Thomas Addis is in considerable measure responsible for the alleged "sterilization" process, in consequence of his pioneer work in this and other problems in renal physiology.

After McLean left the Rockefeller Institute, Van Slyke, working with Austin and Stillman, and later with Möller and McIntosh, showed that the excretory efficiency of the kidney could be expressed simply as *the volume of blood cleared of urea by one minute's excretion*. They called this volume of blood the *urea clearance*. With moderate or abundant diuresis, they found that the kidneys of a normal man excreted on the average the amount of urea contained in 75 cc. of his blood. If the urea content of the blood was increased by urea feeding, the rate of excretion rose parallel with the blood concentration, so that the same 75 cc. of blood were cleared per minute. If the kidneys were damaged by disease, they cleared less blood of urea per minute: in uremia only 3 or 4 cc. or less. The urea clearance was found to be a sensitive clinical measure of renal function. Visualizing, as in a measuring cylinder, the volume of blood which represents the clearance makes it possible to use a mental photograph in place of a mathematical formula.

The clearance is calculated as (mg. urea excreted per minute)/(mg. urea in 1 cc. of blood). If 15 mg. of urea, e.g., are excreted per minute and the blood urea is 0.2 mg. per cc., the clearance is  $15/0.2 = 75$  cc. of blood per minute.

Expressed in terms of the analytical observed values, urine urea concentration,  $U$  and urine volume flow,  $V$ , the urea excretion rate is the product  $UV$ . Indicating blood urea concentration as  $B$ , the clearance assumes the familiar form ordinarily used in its calculation:

$$\text{Clearance} = \frac{UV}{B}$$

If the urine flow fell below about 2 cc. per minute, Van Slyke and his collaborators found that the clearance began to decrease,<sup>13</sup> and between flows of 2 and 0.5 cc. fell approximately in proportion to the square root of the urine volume. In order to use clearances observed with low urine flows as practical measures of renal function it was necessary to correct the observed clearances by multi-

<sup>13</sup> The point at which  $UV$  apparently became proportional to  $B$  (i.e., 2 cc. per minute in man) Austin, Stillman and Van Slyke (4) called the "augmentation limit". This term unfortunately helped to fix the erroneous concept that  $UV/B$  was independent of  $V$  at urine flows above 2 cc. per minute. Actually the relationship of  $UV$  to  $B$  is roughly parabolic, the curve rising rapidly at low urine flows, and gradually flattening and approaching as an asymptote the rate of glomerular filtration at very high urine flows (see 24 and 6).

For Moller, McIntosh and Van Slyke's paper see (18).

plying with the correction  $1/\sqrt{V}$ , when  $V$  was less than 2. Multiplying by this factor gives the volume of blood cleared of urea per minute when the urine flow is 1 cc. per minute. Möller, McIntosh, and Van Slyke called this the "standard clearance," because it applied to a standard urine flow of 1 cc. per minute. It averages 54 cc. of blood in normal men.

$$\text{Standard clearance} = \text{observed clearance} \times \frac{1}{\bar{V}} \quad (a)$$

$$= \frac{UV}{B} \times \frac{1}{\sqrt{\bar{V}}} \quad (b)$$

$$= \frac{U\sqrt{\bar{V}}}{B} \quad (c)$$

To differentiate the higher clearance obtained with abundant urine flows, Möller, McIntosh, and Van Slyke called it the "maximal clearance," since it is the maximum obtainable by accelerating the urine flow.

If in retrospect the square root sign over the  $V$  term in Austin, Stillman and Van Slyke's equation for low urine flows was a compromise with the then inexplicable vagaries of urea excretion, Möller, McIntosh and Van Slyke fully compensated in the direction of rationalism when they borrowed, perhaps from economic bankruptcy, the now familiar term "clearance." Like many good things, this term was born of necessity. In 1926 Van Slyke had been on his way to Baltimore to give an address on kidney function, and on the train his courage failed him when he thought of facing an audience again with a mathematical equation. He had learned what every lecturer must ultimately learn, that only experts can visualize and comprehend the true realities which the unreal symbols of a mathematical equation are intended to represent: the simplest equation has the fearsome power of completely dispelling the comprehension of an audience, at least in the fields of medicine. As Van Slyke sat on the train seeking a solution of how to dispense with mathematics for the benefit of the medical profession, it occurred to him that all that the equation for high urine flows said was that in effect some constant volume of blood was being "cleared" of urea in each minute's time.

In my opinion this word has been more useful to renal physiology than all the equations ever written. In recent years it has broken loose from the excretion of urea and, taking conceptual wings, has become a generalized notion applicable to all aspects of renal excretion. We glibly say that the kidneys *clear* the blood of a large variety of substances: in a particular subject and one minute's time 1.0 cc. of blood may be cleared of water, 10 cc. of sulphate, 20 cc. of potassium, 75 cc. of urea, 130 cc. of inulin, 760 cc. of phenol, 1200 cc. of diodrast, without knowing *a priori* how the kidneys clear the blood of these substances, whether by filtration plus tubular reabsorption, filtration without tubular reabsorption, or filtration plus tubular excretion. Urea is cleared first by separation of some approximately constant quantity of glomerular filtrate, and the reason that the urea clearance decreases with decreasing urine flow is because the more the

tubular urine is concentrated the more urea diffuses back into the blood. Glucose is also filtered, but the *glucose clearance* is normally zero because all the glucose in the tubular urine is reabsorbed; but phlorizin completely blocks the tubular reabsorption of glucose, and in the phlorizinized animal the glucose clearance rises to a large and relatively constant value. If no glucose is secreted by the renal tubules, and if tubular reabsorption is completely blocked, then the rate at which glucose is cleared in the phlorizinized animal must be equal to the rate at which the glomerular filtrate is formed. But the glucose clearance in the phlorizinized animal is identical (in simultaneous observations!) with the *mannitol clearance*, the *sorbitol clearance*, the *dulcitol clearance*, the *creatinine clearance*, the *sucrose clearance*, and the *inulin clearance*; except for glucose and creatinine, these clearances are also identical in the normal animal: hence the conclusion that in the normal animal, mannitol, sorbitol, dulcitol, sucrose and inulin are excreted by filtration alone, and without tubular reabsorption or tubular secretion. Phlorizin blocks the reabsorption of glucose and brings the glucose clearance up to the level of the filtration rate. The creatinine clearance in both the normal and phlorizinized dog is identical with the simultaneous inulin clearance, but in normal man (and apes) the former is about 30 per cent higher, indicating that in addition to filtration, some creatinine is cleared from the blood by the tubules, as is the case in many of the lower animals. Phlorizin blocks this tubular excretion and brings the total creatinine clearance down to the level of the filtration rate.

If, as in the case of creatinine, the clearance of any substance, such as phenol red or diodrast, is greater than the simultaneous inulin or mannitol clearance, it can only be because some of that substance is cleared by the tubules, in addition to that which is cleared through the glomeruli.<sup>14</sup> But there must be a limit even to the process of tubular clearance: we cannot clear any substance from a larger volume of blood than actually perfuses the kidneys. The clearance of diodrast in normal man, calculated as whole blood, is approximately 1200 cc. per minute—one fourth of the total cardiac output. Obviously, this must be close to the total renal blood flow: i.e., the extraction of this compound from the renal blood must be very nearly complete and for practical purposes we may take the diodrast clearance as identical with the renal blood flow.

No elaborate equations are involved in this brief summary—only the notions of filtration plus tubular reabsorption, or filtration plus tubular excretion. The only mathematical operation required is simply to multiply  $U \times V$  and divide by  $P$ .

Paradoxically, Möller, McIntosh and Van Slyke confused the issue by calling  $U\sqrt{V}/B$  a "clearance," since in fact it is the product of a mathematical operation wherein  $UV/B$  is multiplied by  $1/\sqrt{V}$ , as shown in equations (a), (b) and (c) above; hence in the strict sense it is not a real clearance but a presumed clearance predicated on the assumption that below 2.0 cc. per minute  $UV/B$  will

<sup>14</sup> On the premise, of course, that the substance under examination is not synthesized by the kidney, which is certainly true of phenol red, diodrast, p-aminohippuric acid and other substances being studied by renal physiologists.

decrease in proportion to  $1/\sqrt{V}$ , and calculated to the value of  $V = 1.0$ . The widespread use of the calculation without general recognition of its derivation has served to confuse many workers. The "standard clearance" remains a physiological enigma so long as the  $V$  term is under a square root radicle. One of the hardest things students of physiology have to learn is that the two terms:  $UV$ , as they occur in the clearance expression, *must never be divorced*; for by joining them in multiplication they become an integer standing for some *quantity* of a substance excreted per unit time, and you cannot without offence to reason break a *quantity* of anything into two dissimilar parts. Neither can you put a square root sign over half of it.

This, I think was my own first lesson in renal physiology.

William Goldring, who was interested in the etiology of nephritis, had gone to the Rockefeller Institute one day in 1928 to meet Dr. Addis in order to discuss with him the Addis count. He could not find Addis and happened to drift into Van Slyke's laboratory where he was asked to sit down and wait. He and Van Slyke fell to talking about renal function tests, and Van Slyke suggested that Goldring ought to do some urea clearances on patients with erysipelas, of which there were a large number in the Bellevue wards. The results, which have never been published, were very confusing.

During the febrile phase of the disease, the urea clearance might be as much as 200 per cent of the Van Slyke normal standard, and then during the afebrile recovery period they might fall to 30 or 40 per cent of the normal standard. Dr. Goldring could not make any sense out of it, and brought the data to me, knowing that I had been interested in the renal physiology of fishes, turtles and the like. This proved to be poor preparation, and I wrestled with his ever-changing standard clearances and maximal clearances, and got nowhere. Sometimes the patient's standard clearance was greater than his maximal clearance on another occasion, and vice versa. I tried some high-flying mathematics of my own (unable to interpret the physiological significance of the square root radicle in the standard clearance) but to no avail. Perhaps three months elapsed before I fully realized that the maximal clearance might mean something quite simple physiologically, but the standard clearance, because of its square root radicle, was an unphysiological and empirical calculation. The standard clearance apart, I began to think of the maximal clearance simply in terms of filtration rate and tubular reabsorption, as Van Slyke had no doubt thought of it when he first used the term. It was soon evident enough that no physiological interpretation could be forthcoming until there was contained in the experiment some thoroughly reliable, simultaneous measurement of the filtration rate.<sup>15</sup>

<sup>15</sup> Rehberg (20) clearly saw the need of such a standard of reference in 1926; he rather arbitrarily chose creatinine for this purpose, on the grounds that creatinine was concentrated in the urine to a greater extent than any other identified constituent in the urine. Recent work, however, demonstrates that creatinine is in part excreted in man by the tubules. The creatinine clearance has, however, been widely if erroneously accepted by European investigators as identical with the filtration rate.

This led, in 1929, to experiments by Norman Jolliffe, showing that xylose is not excreted by the aglomerular fish, and then to further experiments on the dog and man with Jolliffe and subsequently with James A. Shannon. Our first essay on the measurement of the filtration rate using xylose, sucrose and raffinose proved to be wrong, but we were never wholly content with it, and had sought among other carbohydrates for still larger molecules where there could be no possibility of back diffusion. Sometime in 1933 I hit upon the inulin idea, but a laboratory sample proved to be relatively insoluble and I momentarily discarded it. Fresh inulin was ultimately procured and, in the latter part of the year we got down to work with inulin in a serious manner. We discovered then that we were wrong about xylose as a substance suitable for the measurement of the filtration rate, but we were now more than ever convinced that we were right about inulin.<sup>16</sup>

In October of 1934 Richards came to New York to read a paper on kidney function before the Society of Experimental Biology and Medicine, and we discovered that we were working on the same problems and with the same motives and with the same substance. As far back at 1900 when he had been a student under Philip Hiss, the bacteriologist at Columbia, Richards had suggested inulin to Hiss as a polysaccharide which might yield only levulose for fermentation. If I am not mistaken, an inulin medium is still in use which is based on that suggestion. Thirty years later when he was racking his brain for a substance suitable for the measurement of glomerular filtration, inulin had recurred to him.

With the introduction of the inulin clearance the way was open to study tubular reabsorption and tubular excretion in a quantitative manner. In 1935 Shannon, studying phenol red excretion in the dog, showed, in accordance with the surmise of Marshall and Crane, that at high plasma levels the tubules do indeed become "saturated" and excrete the dye at a constant maximal rate. This maximal limitation in tubular excretion has subsequently been demonstrated for diodrast and a number of other substances in both dog and man, and may be considered to be a characteristic feature of tubular activity.<sup>17</sup>

It was also in 1935 that Goldring, Clark and Smith pointed out that the phenol red clearance at low plasma levels (where the tubules are not approaching saturation) afforded a close approximation to the renal blood flow. At this point Herbert Chasis joined our group, and a little later, Hilmer Ranges. In 1937 Goldring, Chasis and myself showed that the clearance of diodrast, the tubular excretion of which had been demonstrated by Elsom, Bott and Shiels in Richards' laboratory, afforded a closer and indeed quite satisfactory measure of the renal blood flow; and further, that the maximal rate of tubular excretion of diodrast (or diodrast Tm) could be used to characterize the total quantity of functional tubular tissue in the kidneys, independently of the blood flow or

<sup>16</sup> A long series of papers dealing with simultaneous clearances in various species (fishes, dog and man) is reviewed in the "Physiology of the Kidney" (30), in the Porter Lectures (31), and by Smith, Finkelstein and Smith (35).

<sup>17</sup> Tubular excretion has been reviewed by Shannon (25).

filtration rate.<sup>13</sup> In 1938 Shannon, Farber and Troast showed that a similar, limiting maximal rate characterized the reabsorption of glucose by the tubules and, in line with diodrast Tm, they called this term glucose Tm.

The application of the methods for the measurement of blood flow and filtration rate together with the saturation methods (diodrast Tm and glucose Tm), opens new avenues of approach to the study of the distribution of blood or glomerular filtrate among the functional units of the kidney. We can then return, in our study of the human kidney, to the problem of glomerular intermittency, and its corollary of possible intermittency in tubular perfusion, raised by Richards and Schmidt twenty years ago. This problem, with conjoint studies of the effects of disease upon tubular function, comprises the subject matter of the following paper.

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<sup>13</sup> For the application of these methods to man see 9, 32, 33, 34.

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## THE WILLIAM HENRY WELCH LECTURES\*

### II. THE APPLICATION OF SATURATION METHODS TO THE STUDY OF GLOMERULAR AND TUBULAR FUNCTION IN THE HUMAN KIDNEY†

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#### I. INTRODUCTION

In 1924 Richards and Schmidt (28) noted by the direct microscopic observation of the exposed frog's kidney, that in only some of the glomeruli, or in some of the capillaries in individual glomeruli, was the circulation active at any one moment, an observation which has since been confirmed in other cold-blooded animals. It has further been shown that the glomerular circulation can be increased by water diuresis and various drugs, notably caffeine, and decreased by splanchnic stimulation (2, 4, 12, 27, 44). In the frog (15), the alligator (Shannon, unpublished observations) and the marine teleost fishes (9) the rate of glomerular filtration is more or less proportional to the rate of urine formation; while in the marine seal, an animal entirely dependent upon its metabolic water for urine formation, both glomerular filtration and renal blood flow have been shown to increase markedly after the ingestion of food (5, 22). The interrelation between total filtration rate and diuresis in these species indicates that the glomerular circulation is somehow subordinated to physiological control, while in the frog Forster (16) has shown by the application of the glucose saturation method that glomerular intermittency is probably an all or nothing phenomenon.

The notion of intermittent glomerular activity has been transferred to higher animals on the basis of the distribution of dyes injected into the dog and rabbit kidneys (21, 23), but White (45) has concluded that where all the glomeruli of the dog or rabbit are not injected, the unequal distribution of injection fluid is attributable primarily to differences in patency of the larger, preglomerular vessels, rather than inactivity of individual glomeruli, and that under normal conditions all the glomerular vessels are open.

There exist in the human kidney various non-glomerular vascular channels

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which might permit the direct perfusion of the tubules: the chief types of such channels are represented by exceptional terminal or lateral arterioles which terminate directly in the capillary net of the *cortex corticis*, capsular arterioles which penetrate the cortical capillary net, arterioles stemming from the afferent arterioles to make direct connection with the capillary plexus, or Isaacs-Ludwig arterioles, and *arteriolae rectae verae* which pass directly from the interlobular arteries into the medulla; in addition, direct anastomoses connect the arterioles and veins which might permit the arterial perfusion of at least some portions of the peritubular capillary bed by a retrograde capillary perfusion.<sup>1</sup> (For literature, see 34.) All the above connections are relatively rare and probably of negligible importance in the normal kidney, but it is conceivable that in chronic renal disease one or more types of such channels might, by hypertrophy, come to play an important sustaining or excretory rôle. Indeed, Oliver and his collaborators (24) have shown that arterioles of the Isaacs-Ludwig type do hypertrophy in chronic diffuse glomerulonephritis, and by their exquisite reconstructions they have demonstrated the survival of aglomerular nephrons which have the appearance of functional integrity.

Since the function of non-glomerular arterioles, in either the normal or abnormal kidney, must be related to the maintenance of the tubular blood supply when the glomerular circulation is reduced, their potential importance would be considerably enhanced could it be demonstrated that a substantial fraction of the glomeruli in the normal kidney are inactive at any one time. Hence the problems of intermittent glomerular activity and direct tubular blood supply are essentially interdependent. In broader terms, one might argue *a priori* that the well developed renal-portal (venous) circulation to the tubules which characterizes the kidney in the fishes, amphibia, reptiles and birds, would, by sustaining tubular perfusion, favor intermittent glomerular activity; whereas the complete absence of such a renal-portal circulation in the mammals would militate against intermittent activity.

From the physiologic point of view, our interest in the question of the relative distribution of glomerular activity among various nephrons in the kidney is enhanced by the circumstance that the reabsorptive tubule, which is individually fixed in size, is also limited by certain maximal capacities or rates of activity, and it is fair presumption that the quantity of filtrate delivered to each tubule is somehow conditioned by this circumstance. The relative distribution of tubular perfusion is a conjoint problem: were the distribution of peritubular blood subject to control independently of the glomerular circulation, the glomerular-tubular balance could scarcely fail to be impaired.

The present study is an examination of these problems, utilizing two saturation phenomena known to characterize tubules, namely the reabsorption of glucose and the excretion of diodrast. The study naturally divides itself into three parts: first, the application of the saturation methods to the determination

<sup>1</sup> Springorum (39), combining the thermostromuhr method of measuring renal blood flow in the anesthetized dog with simultaneous measurements of blood pressure in the brachial artery and the renal vein, was unable to discover any evidence of functional arterio-venous anastomoses during vasomotor excitation of various types.

of glucose  $T_m$  and diodrast  $T_m$ ; second, the magnitude of these terms in relation to each other and to the filtration rate, in both the normal and diseased kidney—essentially a statistical study of the normal and abnormal parameters or ideal means; and third, the application of the titration method to the frequency distribution problem, wherein glucose saturation is used to determine the distribution of glomerular filtrate, and diodrast saturation is used to determine the distribution of tubular perfusate, among the nephrons of individual subjects.

## II. DESCRIPTION OF THE SATURATION METHODS

### 1. *The reproducibility of glucose $T_m$ and diodrast $T_m$*

Shannon and Fisher (32) and Shannon, Farber and Troast (31) have shown in the dog that as the plasma level of glucose is progressively elevated, a point is ultimately reached where the tubular reabsorption of glucose reaches a constant, maximal rate. Below the minimal level of plasma glucose required to effect tubular saturation, reabsorption from the tubular urine is essentially complete; above this minimal level, such glucose as is filtered through the glomeruli in excess of the maximal rate of reabsorption is excreted in the urine. The maximal rate of reabsorption, as measured for the two kidneys, is in any one animal a reproducible value (31) and is independent of the plasma glucose level between the minimal saturating level (typically about 200 mg. per cent in the dog) and 2000 mg. per cent.

The quantity of glucose filtered per minute constitutes the load of glucose offered to the tubules for reabsorption; for the entire kidneys this load (mg. per min.) is the concentration<sup>2</sup> of glucose in the glomerular filtrate, or  $P_G$  (mg. per cc.), multiplied by the rate of filtration,  $C_{IN}$  (cc. per min.): *i.e.*, glucose load =  $P_G C_{IN}$ . The rate of tubular reabsorption of glucose,  $T_G$  (mg. per min.), is the difference between this load and the quantity of glucose excreted in the urine per minute, or  $U_G V$ :

$$(1) \quad T_G = P_G C_{IN} - U_G V$$

where  $U_G$  (mg. per cc.) is the urine glucose concentration and  $V$  (cc. per min.) is the urine flow. Roughly speaking, as  $P_G$  is increased,  $T_G$  remains equal to  $P_G C_{IN}$  ( $U_G V$  being equal to zero) until the maximal reabsorptive capacity is reached. This maximal rate of tubular reabsorption is designated as glucose  $T_m$ , or  $T_{mG}$ .

Where filtration is arrested completely in a glomerulus, the attached tubule

<sup>2</sup> The concentration of glucose in the glomerular filtrate is greater than in the plasma in consequence of the abstraction of plasma proteins in the filtration process, the true concentration in the filtrate being  $P_G/W$ , where  $W$  equals 1—per cent of plasma protein/100. But since the true filtration rate in cc. of water is  $C_{IN}W$ , the term  $W$  cancels out of all our equations relating to  $T_{mG}$ .

To express all "filtration clearances" in terms of plasma water, in conformity with physiologic fact, would be cumbersome, and, as a matter of convenience, it seems desirable to adhere to the generally accepted convention of expressing them as volumes of plasma, introducing the correction  $W$  only when quantitatively necessary. The correction is necessary in the calculation of tubular excretion of a solute bound to plasma proteins, as in equation (2) of this paper.

will no longer participate in glucose reabsorption and  $Tm_g$  will decrease proportionally, the decrease in  $Tm_g$  being independent of the filtration rate in the remaining nephrons. Short of complete cessation of filtration, the contribution of any unsaturated nephron to  $T_g$  will depend upon the load of glucose being delivered to that nephron, *i.e.*, upon the plasma concentration of glucose and the filtration rate in the attached glomerulus (this circumstance affording the basis for the method developed in Part V of this paper for evaluating the distribution of glomerular activity); but at a concentration of glucose high enough to saturate all nephrons having an average rate of filtration, the gross measurement of  $T_g$  may be expected to afford a rough index of the number of active glomeruli.

In an analogous manner, elevation of the plasma concentration of diodrast leads ultimately to the saturation of the excretory mechanism of the tubules, under which conditions they excrete diodrast at a fixed and reproducible rate (37).

The rate of tubular excretion of diodrast,  $T_D$ , is given by the difference between the total rate of excretion  $U_D V$ , and the rate of diodrast filtration, the latter being given by the product of the plasma concentration,  $P_D$ , times the rate of glomerular filtration,  $C_{IN}$ , times the fraction of free, filterable diodrast in the plasma,  $FW^3$ ; *i.e.*,

$$(2) \quad T_D = U_D V - FW P_D C_{IN}$$

The load of diodrast carried to the tubules must be calculated from the plasma concentration,  $P_D$ , and the renal plasma flow, as estimated from the diodrast clearance,  $C_D$ . For a discussion of this calculation the reader is referred to equation 14. It is sufficient to remark here that when  $P_D$  is high enough to maintain tubular saturation,  $T_D$  has a maximal value and is designated as diodrast  $Tm$ , or  $Tm_D$ .

Complete ischemia of any tubule will result in that tubule dropping out of the process of diodrast excretion, and hence in a proportional decrease in  $Tm_D$ , this decrease being independent of the quantity of blood perfusing other tubules.

## 2. Determination of definitive $Tm_g$

Table I presents data on six normal subjects showing the reproducibility of  $Tm_g$  under standard conditions, either determined on different occasions or at different load/ $T_g$  ratios on the same occasion. In addition, repeated determinations were made on eight of the subjects listed in Table II. Of 20 repeated determinations, 16 agree within 5 per cent, the exceptions being E. B. and H. M. (6 per cent), T. S. (8 per cent), and P. M. (12 per cent).

Shannon and his co-workers (31, 32) have shown in the dog that  $T_g$  does not increase when the load/ $T_g$  ratio is increased from 1.0, or slightly above, to

<sup>3</sup>  $W$  appears in this equation because the nomogram of Smith and Smith (38) relates the equilibrium concentration of free diodrast per 100 cc. of plasma water (ultrafiltrate) to the concentration of total diodrast per 100 cc. of plasma; when the concentration in the filtrate is referred back to plasma, as in the term  $P_D$ , it is diluted by protein to the extent of  $W$ , where  $W = 1.00$ —per cent protein/100.

10.0. In no case have we endeavored to reach such a high ratio as the latter figure and believe that it would be impractical in most subjects, since under these conditions the urine flow is very large and very rapid infusions must be given to prevent dehydration.<sup>4</sup> We do not in general recommend raising  $P_G$  above 700 mg. per cent; in a subject in whom  $C_{IN}$  is relatively high (*e.g.*, 140) and  $Tm_G$  relatively low (*e.g.*, 300) this will yield a load/ $T_G$  ratio of 3.27; but if the above figures are 100 and 400, respectively, this ratio will be only 1.75. Moreover, we have the impression that, unlike the dog where the infusion of glucose at a constant rate tends to produce a progressive increase in  $P_G$ , in man increased utilization or some other factor causes  $P_G$  to level off into a

TABLE I  
*Reproducibility of glucose  $Tm$  in normal subjects*

SUBJECT	DATE	INULIN CLEARANCE	GLUCOSE $Tm$	GLUCOSE LOAD/ $T_G$	$\Delta$ GLUCOSE $Tm$
		<i>cc. per minute</i>	<i>mg. per minute</i>		<i>per cent</i>
J. J.	November 7, 1940	134	313	1.33	
	November 11, 1940	140	313	1.05	$\pm 0.00$
E. B.	September 16, 1940	112	293	1.07	
	September 30, 1940	128	287	1.30	-0.02
C. H.	November 9, 1940	112	277	1.26	-0.06
	September 23, 1940	136	290	1.54	
L. T.	November 4, 1940	129	290	2.41	$\pm 0.00$
	September 20, 1940	91	282	1.18	
T. T.	September 20, 1940	100	270	1.33	-0.04
	November 13, 1940	166	536	1.51	
	November 13, 1940	170	543	1.43	+0.01
	November 13, 1940	173	526	1.17	-0.02
I. N.	January 3, 1941	96	266	1.33	
	January 3, 1941	99	257	1.50	-0.03
	January 3, 1941	98	266	1.66	$\pm 0.00$
	January 3, 1941	108	271	1.90	+0.02
	February 5, 1941	99	265	1.15	$\pm 0.00$

plateau, or even to fall, so that the rate of infusion must be constantly accelerated (from 1.0 up to 4 grams per minute) in order to maintain a steadily ascending curve and to reach plasma concentrations as high as 700 mg. per cent.

<sup>4</sup> The highest urine flow ever observed by us was reached inadvertently while endeavoring to attain a high load/ $T_G$  ratio; the urine flow rose to 41 cc. per minute for twenty minutes ( $P_G = 1400$  mg. per cent) during which time the inulin  $U/P$  ratio was reduced to 3.5. There was moderate cyanosis and considerable subjective discomfort because of dehydration. During forced glycuressis ( $P_G = 500$  to 600 mg. per cent) urine flows as high as 20 to 25 cc. per minute are not infrequent, but rarely exceed 30 cc. per minute (inulin  $U/P$  ratio = 4.0 to 5.0). Such a draft upon the body fluids cannot be sustained for long, though one individual (C.P., 10/27/39) was not incommoded by an average urine flow of 32 cc. for 50 minutes, in spite of an infusion rate of only 6 cc. per minute. In general, urine flows during  $Tm_G$  measurement range from 12 to 20 cc. per minute, with the inulin or mannitol  $U/P$  ratio ranging from 6.5 to 4.0. Equally high urine flows (20 to 30 cc.) may be obtained during  $Tm_D$  measurement, with inulin  $U/P$  ratios ranging down to 4.0, though here such extreme diuresis is much less frequent.

TABLE II

*Glucose Tm and diodrast Tm under the action of adrenalin, hyperemia and caffeine*

The per cent change produced by adrenalin, hyperemia or caffeine is calculated on the basis of the control observation (or the average control value where more than one is shown) immediately preceding the experimental datum in the table.

Column 3, 4, 7 and 9 are corrected to 1.73 sq. m.; column 9 is corrected to 98.5°F. rectal temperature on the assumption that diodrast Tm increases 10 per cent for each degree (F.) of temperature.

SUBJECT	DATE	PLASMA CLEARANCE		FILTRATION FRACTION	GLUCOSE LOAD/T <sub>g</sub>	GLUCOSE T <sub>m</sub>	DIODRAST LOAD/T <sub>D</sub>	DIODRAST T <sub>m</sub>	Δ DIODRAST CLEARANCE	Δ GLUCOSE T <sub>m</sub>	Δ DIODRAST T <sub>m</sub>	
		Inulin	Diodrast									
		C <sub>IN</sub>	C <sub>D</sub>									
		cc. per minute	cc. per minute			mg. per minute		mg. iodine per minute	per cent	per cent	per cent	
P. F.	5/19/38	139	852	16.3			4.55	57.6				Control
	5/30/38	134	604	22.2			2.39	58.7	-29		+2	Adrenalin
	5/25/38	143	1528				2.50	56.3	+79		-2	Hyperemia
J. C.	12/27/38	141	472	29.8			2.39	61.0				Adrenalin
	12/21/38	144	954	15.1			2.81	63.4	+102		+4	Hyperemia
F. A.	1/30/39	113	746	15.2			3.56	53.7				Control
	12/29/38	138	560	24.6			3.76	58.8	-25		+9	Adrenalin
	1/25/39	124	1270	9.8			2.61	53.4	+70		-1	Hyperemia
A. L.	2/17/39	131	854	15.4	1.79	282						Control
	2/17/39	120	542	22.2	1.70	299			-37	+6		Adrenalin
W. S.	2/10/39	148	697	21.2	1.72	338						Control
	2/10/39	139	555	25.1	1.64	360			-20	+6		Adrenalin
E. M.	3/ 1/39	129	666	19.4	1.74	344	2.99	48.7				Control
	1/26/39	128	808	15.8			3.97	45.8	+21		-6	Hyperemia
	3/ 8/39	111	847	13.2	1.81	332	8.15	44.5	+26	-3	-9	Hyperemia
J. J.	12/22/38	126	746				2.50	51.0	+12		+5	Hyperemia
	3/15/39	162	946	17.1	1.84	385	7.12	56.4				Control
	4/14/39	198			2.13	374						Control
	3/24/39	146	1655	8.8	1.79	416	16.4	54.1	+75	+10	-4	Hyperemia
H. M.	4/ 5/39	146	757	19.3	2.25	372	4.83	64.5	-20	-2	+14	Adrenalin
	6/ 2/39	150			1.79	431						Control
	6/ 2/39	140			1.88	450				+4		Adrenalin
	6/14/39	138			1.63	455	3.02	65.7				Control
	6/14/39	129			1.68	458	2.16	64.2		+1	-2	Adrenalin
J. Hu	5/10/39	154	1090	13.5	1.61	400				-12		Hyperemia
	2/13/39	128	714	17.9	1.30	319						Control
	2/13/39	138	602	22.9	1.18	316			-16	-1		Caffeine
	2/20/39	124	752	16.5	1.37	322						Control
	2/20/39	126			1.19	299	4.32	40.3				Control
C. C.	2/27/39	137	655	21.7	1.45	336	8.25	43.2	-13	+8	+7	Caffeine
	3/ 3/39	129	950	13.1	1.57	338	8.42	42.2	+26	+9	+5	Hyperemia
	5/15/39	181	705	25.7	1.27	415	4.98	64.3				Control
	5/29/39	141			1.53	417						Control
	6/29/39	134			1.91	349	4.02	63.7				Control
	6/29/39	161			2.18	342	3.40	64.2		-13	±0	Caffeine
	5/22/39	147	818	18.0	1.58	392	6.72	60.6	+16	-1	-5	Hyperemia
	6/ 7/39	147	930	15.8	1.92	390	5.78	63.6	+32	-1	-1	Hyperemia

TABLE II—Continued

SUBJECT	DATE	PLASMA CLEARANCE		FILTRATION FRACTION	GLUCOSE LOAD/ $T_G$	GLUCOSE $T_m$	DIODRAST LOAD/ $T_D$	DIODRAST $T_m$	$\Delta$ DIODRAST CLEARANCE	$\Delta$ GLUCOSE $T_m$	$\Delta$ DIODRAST $T_m$	
		Inulin $C_{IN}$	Diodrast $C_D$									
		cc. per minute	cc. per minute			mg. per minute		mg. iodine per minute	per cent	per cent	per cent	
R. D.	2/24/39	135	920		1.21	356	3.85	58.7				Control
	3/ 6/39	137	1302				9.45	46.2	+42		-21	Hyperemia
	6/ 9/39	117			1.25	351	2.06	59.8				Control
	6/ 9/39	140			1.10	377	1.85	54.0		+7	-10	Caffeine
	6/15/39	117					2.26	51.8				Control
	6/15/39	122					2.24	45.4			-12	Caffeine
J. B.	6/28/39	127			1.44	309	4.27	59.7				Control
	6/28/39	139			1.40	319	5.32	59.4		+3	-1	Caffeine
T. S.	10/18/39	156			1.74	344	2.02	57.5				Control
	10/18/39	157			1.73	394	1.73	55.4		+15	-4	Adrenalin
	10/25/39	138			1.77	317	2.58	57.0		-8		Control
C. P.	10/20/39	160			1.63	416	1.86	58.2				Control
	10/20/39	119			2.50	213	1.44	55.4		-49	-5	Adrenalin
	10/27/39	161			1.75	420	3.55	56.7				Control
	11/ 3/39	164	904		1.76	424						Control
P. M.	10/16/39	119			1.82	246	1.19	62.4				Control
	10/16/39	126			2.22	267	1.22	52.5		+9	-16	Adrenalin
	10/11/39	93			1.92	227	3.21	55.3				Control
	10/11/39	128			3.09	207	3.50	51.9		-9	-6	Caffeine
	10/23/39	114			1.74	257	2.89	59.4				Control

Even under these conditions  $U_G V$  may not exceed 0.25 grams per minute. The great capacity of the body to dispose of glucose by storage or utilization presents one of the chief difficulties in the glucose titration method.

In most of the control observations in Tables I and II the load/ $T_G$  ratio has not varied greatly in the several observations, (this difference being greater than 0.3 only in C. H., T. T., and I. N.), but a wider spread is available in the various experimental observations in Table II; since  $T_G$  did not change under the experimental conditions there recorded, we believe these data may be considered as supplementing the data in Table I, from which we infer that definitive  $T_{m_G}$  is generally reached in the normal kidney at a load/ $T_G$  ratio of 1.25, and that no increase in  $T_G$  is to be expected at higher levels.<sup>5</sup>

<sup>5</sup> In a previous report we believed that glucose reabsorption had a perceptible temperature coefficient, like the tubular excretion of diodrast (19). Subsequent observations have caused us to doubt this view; the question is not readily examined experimentally, but we feel that for the present it is advisable to omit temperature corrections and to present the data as observed. Consequently certain data on  $T_{m_G}$  from Table III of our previous paper (19) are again presented here, uncorrected for temperature, while other data in that table are excluded from the present report on the grounds that the load/ $T_G$  ratio is not high enough to insure saturation. The present data may be taken as replacing the previous table entirely.

### 3. Determination of definitive $Tm_D$

The elevation of the plasma concentration of diodrast to levels at which all tubules are saturated (load/ $T_D$  ratio greater than 2.0) is a relatively easy matter, but experience has taught us that the injection of large quantities of diodrast solution is apt to temporarily reduce  $Tm_D$ , probably by causing vasoconstriction of some of the renal arterioles. The reaction is unusual, however, if the priming injection of diodrast is administered slowly.

### 4. Independence of tubular reabsorption and tubular excretion

To answer the question whether tubular reabsorption (glucose) is physiologically independent of tubular excretion (diodrast), we have measured these terms both simultaneously and independently in several subjects. In no case have we found that either value is affected by saturation of the other system.<sup>6</sup> In view of the above fact,  $Tm_G$  and  $Tm_D$  may be determined simultaneously, as has been done in some instances in Table II. The double procedure is not recommended, however, since it offers opportunities for unanticipated complications.

### 5. The reproducibility of $Tm_G$ and $Tm_D$ , as examined by adrenalin, caffeine and pyrogenic hyperemia

The present section is an inquiry into the question of whether  $Tm_G$  and  $Tm_D$  are influenced by drugs which alter the effective renal blood flow, as measured by the diodrast clearance (see Table II). In such an examination it is desirable to have some knowledge of the extent to which these agents have altered the renal blood flow. Since saturation of the tubules with respect to the reabsorption of glucose does not interfere with the tubular excretion of diodrast, the diodrast clearance can be followed simultaneously with the measurement of  $Tm_G$  for eight to ten successive clearance periods, the drug being administered at the middle of the series. (Examples of this procedure are given in Table II in the observations on A. L., W. S., etc.) If no information is desired on the diodrast clearance, *i.e.*, if the action of the drug on the renal blood flow is to be inferred from separate observations made under comparable conditions,  $Tm_D$  may similarly be followed throughout the "control" and "experimental" observations. (See H. M., June 14, 1939.) Or the "control" and "experimental" observations on  $Tm_D$  may be made on different occasions, as in the case of P. F., J. C., etc. This has been the invariable procedure in the study of pyrogenic hyperemia, since it was desirable to observe both the diodrast clearance and  $Tm_D$  during the hyperemic state, in order to determine to what extent the renal blood flow had been increased by the pyrogen.

*Adrenalin.* The action of adrenalin on the renal circulation in man has been

<sup>6</sup> Substances which are excreted by the tubules (phenol red, diodrast, hippuran and other hippuric acid derivatives (13)) do interfere with the simultaneous excretion of each other; while xylose and galactose interfere with the reabsorption of glucose (29). Since both the (glucose) reabsorptive and excretory process are probably localized in the proximal tubule, it appears that systems which are chemically independent of each other may be localized in the same nephron segment, and possibly in the same tubule cell.

discussed elsewhere (7). Adrenalin reduces the effective renal plasma flow by constriction of the efferent glomerular arterioles. The dose usually employed here has been 0.5 mg. subcutaneously plus 0.5 mg. intramuscularly, though occasionally where there was no marked effect on blood pressure a supplementary dose of 0.5 mg. intramuscularly has been given about twenty minutes later in order to maintain the action through the whole period of renal observation. The diodrast clearance was followed in P. F., F. A., W. S. and J. J. and was consistently reduced ( $-29$ ,  $-25$ ,  $-37$ ,  $-20$  and  $-20$  per cent), confirming our previous experience.

$\Delta Tm_g = +6$ ,  $+6$ ,  $-2$ ,  $+4$ ,  $+1$ ,  $+15$  (T. S.) and  $+9$  per cent (average net  $\Delta = +6$  per cent). The preponderance of changes in the positive direction might indicate that adrenalin increases the filtration rate in a few glomeruli in which this rate is normally too low to effect tubular saturation at the load/ $T_g$  ratios used, but the series as a whole shows that the proportion of such nephrons is small. It can certainly be concluded that adrenalin does not close any glomeruli, in spite of a marked reduction in total blood flow.

(Subject C. P. received a supplementary intramuscular injection of 0.5 mg. of adrenalin 20 minutes after the first divided dose, and showed a decrease of 49 per cent in  $Tm_g$ —i.e., a large number of glomeruli were apparently closed by the drug. Since the filtration rate dropped 26 per cent, it appears that widespread afferent constriction occurred. There were no exceptional objective symptoms and no subjective complaints. This is the only time a response of this type has occurred in many observations on adrenalin and we consider it atypical, at least for moderate doses.)

$\Delta Tm_D = +2$ ,  $+9$ ,  $+14$ ,  $-2$ ,  $-4$ ,  $-5$  and  $-16$  per cent (average net  $\Delta =$  nil). Although two of these changes are large, they are in opposite directions, and the other changes are also inconsistent. We conclude, therefore, that adrenalin does not bring into or exclude from perfusion any substantial quantity of tubular tissue.

*Caffeine.* The xanthine derivatives have a complex effect upon the renal circulation; there is a delayed reduction in renal blood flow which appears to be an indirect effect of the drug upon the efferent glomerular arterioles, mediated perhaps through increased sympathetic tone; and there is generally a slow, progressive, but slight increase in filtration rate which, since the mean arterial pressure is not greatly increased, may represent slight dilatation of the afferent glomerular arterioles (7). Although theophylline is more popular in clinical use, partly because it has less central effect, caffeine is the substance which has been demonstrated to increase the glomerular circulation in cold-blooded animals and we have therefore used caffeine throughout this study. The dose has ranged from 1.0 gram intramuscularly and 1.0 gram intravenously of caffeine sodium benzoate down to half this amount. The diodrast clearance was followed in two instances only (both on J. Hu.), and showed a decrease ( $-16$  and  $-13$  per cent), while the filtration rate consistently increased ( $+8$ ,  $+9$ ,  $+20$ ,  $+4$ ,  $+38$  and  $+9$  per cent, average net change  $= +15$  per cent), both results being in agreement with our previous study.

$\Delta Tm_g = -1$ ,  $+8$ ,  $-13$ ,  $+7$ ,  $+3$  and  $-9$  per cent (average net  $\Delta = -1$

per cent). The failure of  $Tm_G$  to increase consistently at a time when the total filtration rate is increased indicates that caffeine does not increase the filtration rate in any significant number of glomeruli in which this rate is so low as to prevent saturation of the tubules at the load/ $T_G$  ratio used.

$\Delta Tm_D = +7, \pm 0, -10, -12, -1$  and  $-6$  per cent (average net  $\Delta = -8$  per cent). Two of these results ( $-10$  and  $-12$  per cent) were obtained in a subject R. D., in whom  $Tm_D$  has shown marked changes in control observations (51.8 to 59.8), and we suspect that this is an example of spontaneous changes in intrinsic tubular activity of unknown origin, such as are discussed in connection with renal function in hypertensive subjects (19). Excluding this subject, the other changes are so slight as to indicate that caffeine does not disturb tubular perfusion.

*Hyperemia.* Renal hyperemia (7) was induced by the intravenous injection of pyrogenic inulin of known potency (Lot No. 268). In every case the subject was premedicated with amidopyrine (10 grains every four hours for 16 to 24 hours before the test) in order to block autonomic disturbances other than the renal response. The diodrast clearance was followed in most instances and generally increased markedly ( $+79, +70, +21, +12, +75, +26, +16, +32$  and  $+41$  per cent, with an extreme difference in J. C., as between adrenalin and hyperemia, of  $+102$  per cent).

$\Delta Tm_G = -3, +10, -12, +9, -1$  and  $-1$  (average net  $\Delta = +2$  per cent). That  $Tm_G$  changes so little indicates that pyrogenic hyperemia (efferent arteriolar dilatation) does not increase activity in any subactive glomeruli.

$\Delta Tm_D = -2, +4, -1, -6, -9, +5, -4, +5, -5, -1, -21$  per cent (average net  $\Delta = -3$  per cent). The single large change ( $-21$  per cent) is again in R. D., and may reflect a spontaneous rather than an experimentally induced change. The slight changes in other instances indicate that renal hyperemia does not bring under perfusion any unperfused tubules in the normal kidney. (This is not the case in some subjects with essential hypertension (20).

*Discussion.* Were any appreciable number of glomeruli in the normal kidney inactive, or prone to pass into a state of low activity by virtue of normal intermittency, we believe that one or all of these methods of examination would have revealed changes in  $Tm_G$  of a much larger order of magnitude than those observed. It is true that in the case of both adrenalin ischemia and pyrogenic hyperemia, the chief locus of action on the renal vascular tree appears to be beyond the glomeruli, presumably in the efferent glomerular arterioles; and it is possible that constriction of the efferent arteriole would not arrest filtration in an otherwise active glomerulus, while efferent dilatation would not permit restoration of activity in a previously inactive glomerulus; but it is difficult to believe that such marked changes in total renal blood flow would fail to disturb a pattern of intermittent activity involving any large number of glomeruli, were such intermittent activity present. The argument is more cogent in the case of caffeine, which increases the total filtration rate: the failure of this drug to increase  $Tm_G$  is very strong evidence against intermittent glomerular activity.

Diodrast  $Tm$  refers to the number of "active" tubules which are perfused at

any moment. We have elsewhere (35) remarked on the possible importance of the circulation of interstitial fluid in the perfusion of the tubules (see also p. 94); if this presupposition is credited, it is perhaps not to be expected that marked changes in renal blood flow would result in significant changes in the perfusion of tubular tissue, since the continued circulation of interstitial fluid would tend to maintain tubular perfusion even where some glomeruli were inactive. But it is equally possible that the perfusion of the tubules is strictly dependent on the perfusion of the glomeruli, and that our failure to modify  $Tm_D$  is contingent upon the circumstance that glomerular activity is uniformly maintained under all the above conditions.

In any case, the above results, in showing that the number of nephrons reabsorbing glucose at moderate load/ $T_G$  ratios is not increased by circumstances which greatly increase glomerular pressure (adrenalin and caffeine) or total renal blood flow (hyperemia), controvert the idea, carried into mammalian physiology from observations on cold-blooded animals, that any significant number of glomeruli are inactive at any moment.

### III. COMPARISON OF $Tm_G$ AND $Tm_D$ IN NORMAL SUBJECTS

The foregoing studies, carried out under conditions representing the most vigorous vascular changes readily induced in the human kidney, afford increased confidence in the significance of the data obtained by the use of the glucose and diodrast saturation methods. The reproducibility of  $Tm_G$  and  $Tm_D$  is such that we may proceed on the premise that the intrinsic activity of both the reabsorptive and excretory mechanisms of the tubules is essentially stable and amenable to adequate measurement. (The reader is cautioned that certain procedures can of course close the glomeruli, or acutely reduce perfusion of the tubules, and a subsequent section of this paper is devoted to precautions which must be taken in this respect.)

This intrinsic stability leads to the expectation that a comparison of the two saturation methods in the diseased kidney may afford information on the effects of disease on specific tubular processes.<sup>7</sup> For this comparison a knowledge of the normal statistical parameters is of course necessary, and consequently the available normal data are summarized in Table III. Other pertinent data on the filtration rate ( $C_{IN}$ ), diodrast clearance ( $C_D$ ), etc., are included for completeness.

The data on normal subjects in Table III are divided into the "old series" presented in a previous paper (19), the "new series" here presented for the first time, and a "combined series" in which all data are treated together.<sup>8</sup> In the

<sup>7</sup> One of course cannot generalize from the reabsorption of glucose to the reabsorption of chloride, water or other substances, since entirely different reabsorptive mechanisms are involved; nor from the excretion of diodrast to the excretion of other substances which may be handled by wholly independent mechanisms. As renal physiology increasingly develops quantitative methods and modes of thought the reiteration of these qualifications becomes increasingly superfluous.

<sup>8</sup> We are greatly indebted to Mr. Charles Sternheel for the statistical analysis of the new and combined series.

TABLE III

*Glucose Tm and diodrast Tm in normal subjects*

Each datum in columns 5, 6, 7, 8 and 9 represents the average of three or more clearance periods, and is corrected to 1.73 sq. m.; column 8 is corrected to 98.5°F.

SUBJECT	AGE	SURFACE AREA	DATE	PLASMA CLEARANCE		EFFECTIVE BLOOD FLOW	DIODRAST <i>T</i> <sub>m</sub>	GLUCOSE <i>T</i> <sub>m</sub>	INULIN CLEARANCE/ GLUCOSE <i>T</i> <sub>m</sub>	DIODRAST CLEARANCE/ GLUCOSE <i>T</i> <sub>m</sub>	GLUCOSE <i>T</i> <sub>m</sub> /DIODRAST <i>T</i> <sub>m</sub>	INULIN CLEARANCE/ DIODRAST <i>T</i> <sub>m</sub>	DIODRAST CLEARANCE/ DIODRAST <i>T</i> <sub>m</sub>	INULIN CLEARANCE/ DIODRAST CLEARANCE
				Inulin	Diodrast									
Men														
		sq. m.		cc. per minute	cc. per minute	cc. per minute	mg. iodine per minute	mg. per minute						
W. S.	48	1.52	2 10/39	148	697	1200		338	0.438	2.06				21.2
J. Hu	39	1.85	2/13/39	128	714	1210	40.3	315	0.406	2.27	7.82	3.18	17.7	17.9
A. L.	42	1.88	2 17/39	131	854	1690		282	0.465	3.03				15.3
E. Mc	50	1.84	3 1 39	129	666	1044	45.1	342	0.377	1.95	7.58	2.86	14.8	19.4
J. J.	28	1.65	3 15/39	162	946	1505	58.3	380	0.426	2.49	6.52	2.78	16.2	17.1
C. C.	42	1.77	5 15/39	150	705	1320	64.0	383	0.392	1.84	5.99	2.34	11.0	21.3
R. D.	28	1.98	6 9 39	117			56.8	354	0.331		6.23	2.06		
H. M.	34	1.81	6 14 39	144			65.7	443	0.325		6.74	2.19		
J. B.	45	1.48	6/28 39	127			59.7	309	0.411		5.18	2.13		
P. M.	36	1.72	10 16 39	109			59.0	243	0.448		4.12	1.85		
T. S.	37	1.70	10 18 39	147			57.3	330	0.445		5.76	2.57		
C. P.	34	1.67	10/20 39	162			57.5	420	0.386		7.30	2.82		
T. T.	32	1.62	12 4 40	166	704	1043	53.4	536	0.310	1.31	10.04	3.11	13.2	23.6
W. F.	31	1.77	12 18 40	136	654	1063	48.0	477	0.285	1.37	9.94	2.83	13.6	20.8
I. N.	34	1.53	1 3 41	100	389	635	32.0	269	0.372	1.45	8.41	3.13	12.2	25.7
P. H.	52	1.80	1 13 41	152	784	1387	44.1	380	0.400	2.06	8.62	3.45	17.8	19.4
W. Mc	40	1.77	1 27 41	173	943	1685		580	0.298	1.63				18.3
J. Bg	49	1.76	3/21 41	112	674	1262	44.1	269	0.416	2.51	6.10	2.54	15.3	16.6
W. O.	48	1.88	3 31 41	128	845	1496	42.5	380	0.337	2.22	8.94	3.01	19.9	15.1
H. B.	58	1.77	4 2 41	114	649	1152	47.2	437	0.261	1.49	9.26	2.42	13.8	17.6
M. D.	60	1.73	4 7 41	138	664	1072	56.4	406	0.340	1.64	7.20	2.45	11.8	20.8
J. L.	39	1.91	4 14 41	116	562	1047	49.6	396	0.293	1.49	7.98	2.34	11.9	19.6
J. W.	45	1.73	5 26 41	152	876	1753	49.8	380	0.400	2.31	7.63	3.05	17.6	17.4
J. R.	39	1.59	6 16 41	123	578	1040	56.0	353	0.348	1.64	6.30	2.20	10.3	21.3

## Present series, normal men

n		24	18	18	21	24	24	18	21	21	15	18
Mean		136	719	1256	51.8	375	0.371	1.93	7.32	2.63	14.5	0.193
$\sigma$		19.3	134.9	280.3	8.30	79.7	0.0563	0.490	1.51	0.422	2.77	0.0266
$\sigma_m$		3.94	31.8	66.1	1.81	16.3	0.0115	0.108	0.330	0.092	0.715	0.0063
r							0.656	0.323	0.235	0.430	0.366	
100 $\sigma_m$		14.2	18.8	22.3	16.0	21.2	15.2	23.8	20.6	16.0	19.1	13.8

## Original series, normal men

n		54	43	43	26				26	19	43
Mean		130	688	1189	53.3				2.57	13.6	0.189
$\sigma$		21.7	135.3	242.4	9.1				0.28	1.4	0.024
$\sigma_m$		2.96	20.6	36.9	1.8				0.055	0.32	0.0036
r									0.77	0.77	
100 $\sigma_m$		16.7	19.7	20.4	17.1				10.9	10.3	12.7

TABLE III—*Concluded*

SUBJECT	AGE	SUR- FACE AREA	DATE	PLASMA CLEARANCE		EFFECTIVE BLOOD FLOW	DIODRAST $T_m$	GLUCOSE $T_m$	INULIN CLEARANCE/ GLUCOSE $T_m$	DIODRAST CLEARANCE/ GLUCOSE $T_m$	GLUCOSE $T_m$ /DIODRAST $T_m$	INULIN CLEARANCE/ DIODRAST $T_m$	DIODRAST CLEARANCE/ DIODRAST $T_m$	INULIN CLEARANCE/ DIODRAST CLEARANCE
				Inulin	Diodrast									
Combined series, normal men														
$n$				cc. per min- ute	cc. per min- ute	cc. per min- ute	mg. iodine per min- ute	mg. per min- ute						
Mean				67	61	61	40	24	24	18	21	40	34	61
$\sigma$				131	697	1209	51.8	375	0.371	1.93	7.32	2.63	14.0	0.190
$\sigma_m$				21.5	135.9	255.9	8.73	79.7	0.0563	0.460	1.51	0.344	2.16	0.0244
$r$				2.63	17.4	32.8	1.38	16.3	0.0115	0.108	0.330	0.054	0.370	0.0031
100 $\sigma/m$				16.4	19.5	21.2	16.8	21.2	15.2	23.8	20.6	13.1	15.4	12.8
Women														
		sq. m.												
J. Ha	50	1.72	12/ 2/40	135	567	886		445	0.303	1.27				23.8
H. P.	16	1.73	3/24/41	116	682	1137	35.8	349	0.333	1.95	9.75	3.24	19.0	17.0
M. M.	31	1.49	3/28/41	104	344	565	24.0	280	0.372	1.23	11.66	4.34	14.3	30.2
A. C.	45	1.68	6/ 2/41	123	724	1234	40.9	280	0.439	2.59	6.85	3.01	17.7	17.0
V. P.	26	1.63	6/ 4/41	115	650	1054	40.1	283	0.407	2.30	7.06	2.87	16.2	17.7
C. V.	35	1.73	6/23/41	106	537	926	34.7	212	0.500	2.53	6.11	3.06	15.5	19.7
E. B.	24	1.53	9/16/40	117				283	0.414					
L. T.	51	1.57	9/20/40	92				276	0.333					
C. H.	33	1.44	9/23/40	134				290	0.463					
R. P.	55	1.84	8/ 2/40	106				319	0.332					
J. J.	17	1.75	8/ 7/41					313	0.451					
Present series, normal women														
$n$				10	6	6	5	11	11	6	5	5	5	6
Mean				115	584	967	35.1	303	0.395	1.98	8.29	3.30	16.5	0.209
$\sigma$				12.8	124.9	215.1	6.04	55.3	0.0617	0.554	2.09	0.531	1.65	0.0478
$\sigma_m$				4.05	51.0	87.8	2.70	16.7	0.0186	0.226	0.934	0.237	0.738	0.0195
$r$									0.048	0.135	0.069	0.818	0.944	
100 $\sigma/m$				11.1	21.4	22.2	17.2	18.3	15.6	28.0	25.2	16.1	10.0	22.9
Original series, normal women														
$n$				11	11	11	9					9	9	11
Mean				118.7	600.4	996	46.7					2.54	12.8	0.198
$\sigma$				17.5	87.0	162.7	8.5					0.28	1.52	0.014
$\sigma_m$				5.28	26.2	49.1	2.83					0.125	0.68	0.0042
100 $\sigma/m$				14.7	14.5	16.3	18.2					11.0	11.9	7.1
Combined series, normal women														
$n$				21	17	17	14	11	11	6	5	14	14	17
Mean				117	594	982	42.6	303	0.395	1.98	8.29	2.81	14.2	0.202
$\sigma$				15.6	102.4	184.4	9.46	55.3	0.0617	0.554	2.09	0.555	2.36	0.0310
$\sigma_m$				3.40	24.8	44.7	2.53	16.7	0.0186	0.226	0.934	0.148	0.631	0.0075
$r$									0.048	0.135	0.069	0.674	0.603	
100 $\sigma/m$				13.3	17.2	18.8	22.2	18.2	15.6	28.0	25.2	19.7	16.6	15.3

statistical analysis our old data on  $Tm_G$  are wholly replaced by those of the present paper, for reasons cited earlier; and since each subject is counted only once, certain duplications in  $C_{IN}$  and  $Tm_D$  are omitted, chiefly from among those subjects who appeared in our previously published Table III (19).

Examination of the summaries in our present Table III shows that the means of the new and old series are in good agreement, especially among the men where the numbers of individuals are larger. The correlation coefficient,  $r$ , between  $C_{IN}$  and  $Tm_D$  and between  $C_D$  and  $Tm_D$  is lower among men in the new series, but remains good in the combined series in both sexes, bearing out the usefulness

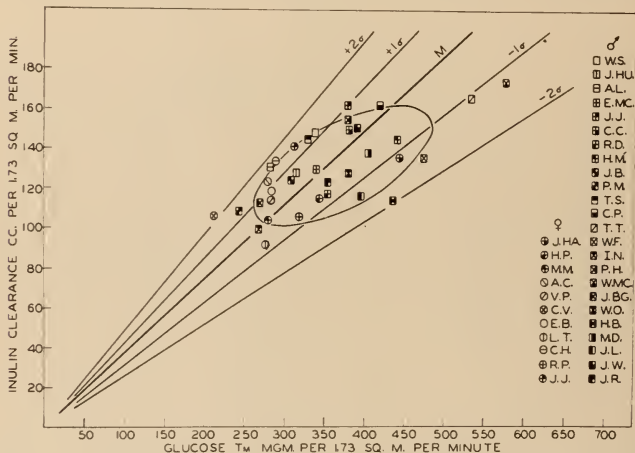


FIG. 1. Inulin Clearance ( $C_{IN}$  or Filtration Rate) in Normal Subjects, Related to Glucose  $Tm$  ( $Tm_G$  or Maximal Rate of Glucose Reabsorption).

The statistical background,  $M$ , is the mean ratio  $C_{IN}/Tm_G$ ,  $\pm$  multiples of the standard deviation. The ellipse is calculated (20, see also note at end of this paper) to contain 70 per cent of the observations, and actually contains 71 per cent.

of  $Tm_D$  as an index of the quantity of functional tissue to which to refer  $C_{IN}$  and  $C_D$ .

With the increase in the number of data on women, it has seemed desirable to separate the two sexes and use the specific sex data for future reference, especially since in every case the means are significantly smaller in women than in men. In all statistical references in this paper the appropriate sex standards, as cited under the combined series, are used.

One major purpose of this study concerns the relation of  $Tm_G$  to other renal functions, and it will be observed in Table III that this term has a significantly positive correlation (0.656) only with  $C_{IN}$  among the men, the correlation with  $Tm_D$  and  $C_D$  being so low (0.323 and 0.235) as to be questionable. Among the

women,  $C_{IN}$  and  $Tm_G$  show no correlation, but we believe that this may be fortuitously related to the small sample. As the reader will see in Figure 1, both terms have a relatively narrow dispersion, which circumstance contributes some uncertainty to the coefficient of correlation; while the dispersion in the case of women is even narrower. In neither case is the series large enough to warrant confident conclusions, but the data indicate that  $Tm_G$  is positively correlated with  $C_{IN}$  in men (and by inference we believe this to be true of women) (fig. 1): *i.e.*, the tubular reabsorptive capacity is roughly proportional to the filtration rate.

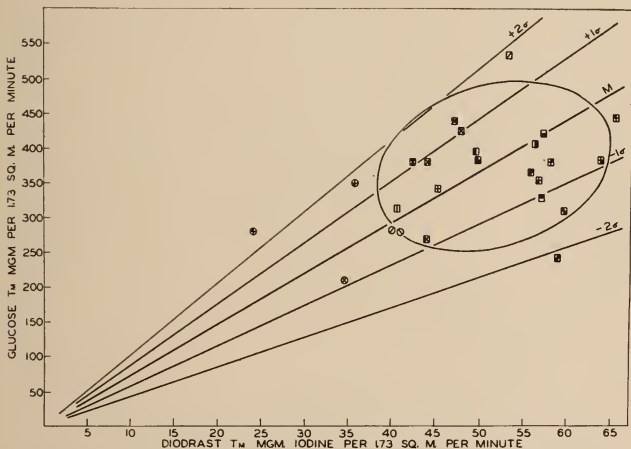


FIG. 2. Glucose  $Tm$  in Normal Subjects, Related to Diodrast  $Tm$  (Maximal Rate of Tubular Excretion).

The statistical background,  $M$ , is the mean ratio  $Tm_G/Tm_D \pm$  multiples of the standard deviation. The ellipse is calculated to contain 70 per cent of the observations, and actually contains 72 per cent.

The correlation between  $Tm_G$  and  $Tm_D$  is relatively poor: *i.e.*, the tubular reabsorptive capacity bears little or no relation to the tubular excretory capacity, as is shown in Figure 2.

A positive correlation between  $C_{IN}$  and  $Tm_G$  is rather to be anticipated, in view of the functional relationship which, in the interests of glucose conservation, we may expect to find between any glomerulus and its nephron. *A priori*, there is no reason to expect that glucose reabsorption would have any functional relationship to renal blood flow or tubular excretion, and hence the poorer correlation of  $Tm_G$  with  $C_D$  and  $Tm_D$  is not surprising. This poor correlation shows that the reabsorptive and excretory activities of a tubule, even where these are probably localized in the same segment, may be developed to quite

different functional levels, and reveals the precariousness of judging tubular functional capacity by one index, and especially by cytological appearance.

#### IV. COMPARISON OF $Tm_G$ AND $Tm_D$ IN HYPERTENSIVE SUBJECTS

In our previous paper on renal function in subjects with essential hypertension (20), we recorded our conclusion that during the progress of this disease the excretory capacity of the tubules for diodrast is impaired, leading to a reduction in  $Tm_D$ . Since in some subjects the ratio  $C_{IN}/Tm_D$  had values far in excess of

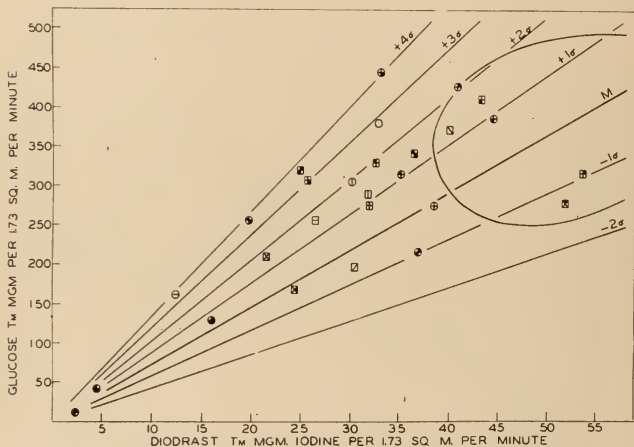


FIG. 3. Glucose  $Tm$  in Hypertensive Subjects, Related to Diodrast  $Tm$

The statistical background is the normal mean ( $M$ ) ratio  $Tm_G/Tm_D$ ,  $\pm$  multiples of the standard deviation, as shown in Figure 2. Most of the observations are low in respect to the normal value of  $Tm_D$ , but normal in respect to the value of  $Tm_G$ . Hence 74 per cent fall above the mean ratio,  $M$ . I. e.,  $Tm_D$  may be decreased markedly in hypertensive subjects, while  $Tm_G$  is essentially normal. The term "impotent" has been used to describe tubules which have lost the power of excreting diodrast, but which remain connected to functional glomeruli: the trend depicted here indicates that such "impotent" tubules can reabsorb glucose.

normal, we inferred that this loss of excretory capacity might occur without obliteration of the glomerulus or occlusion of the tubule in a certain fraction of nephrons, leading to the formation of what we called "impotent" nephrons. (We recognized that increased glomerular pressure associated with elevated blood pressure could produce the same effect, and that there was available in the study referred to no certain means of differentiating these factors; nevertheless the general relations of the data led us to place the emphasis on tubular impotence rather than increased glomerular pressure.)

It is of special interest then to observe the relative values of  $Tm_G$  and  $Tm_D$

in hypertensive subjects. Data pertinent to this question are given in Table IV and Figures 3 and 4. These data show that:

1) In the hypertensive kidney  $Tm_D$  may suffer marked reduction while  $Tm_G$  tends to remain within the normal limits of 200–450 mg. per minute. This is well displayed by the scatter diagram of Figure 3, which is to be compared with Figure 2 for the normal distribution. It will be seen from Figure 3 that the ratio  $Tm_G/Tm_D$  for most subjects lies well above the normal mean ( $M$ ), in consequence primarily of a reduction in  $Tm_D$  rather than in consequence of an increase in  $Tm_G$ .

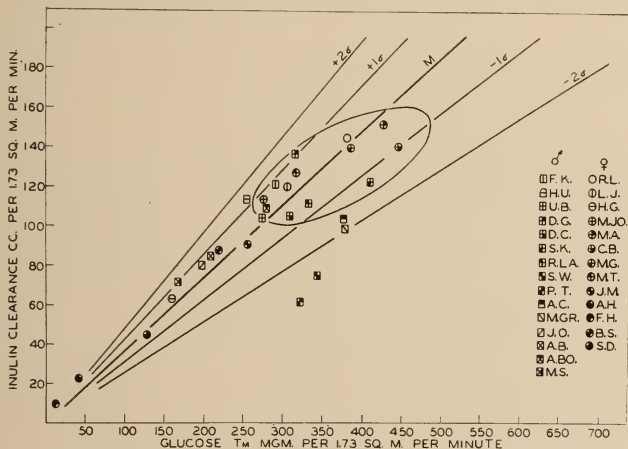


FIG. 4. Inulin Clearance in Hypertensive Subjects, Related to Glucose  $Tm$

The statistical background is the normal mean ( $M$ ) ratio  $C_{IN}/Tm_G$ ,  $\pm$  standard deviation, as shown in Figure 1. Although both  $C_{IN}$  and  $Tm_G$  tend to fall below the mean normal values, the ratio  $C_{IN}/Tm_G$  is maintained at its normal value, indicating that  $Tm_G$  is not specifically affected by the disease, but is decreased only in consequence of reduction of  $C_{IN}$ . I.e., as glomeruli are deleted from the kidney by arteriolar or glomerular lesions, the attached tubules necessarily drop out of glucose reabsorption, but glucose reabsorption *per se* is not impaired by hypertensive disease.

In two subjects (S. W. and P. T.) the filtration rate is excessively low, perhaps reflecting thickening of the glomerular membranes or some other impediment to filtration, not typically present in the other subjects.

2)  $Tm_G$  and  $C_{IN}$  maintain an almost *precisely normal proportional ratio* in the hypertensive kidney, as is shown by Figure 4, from which fact we infer that  $Tm_G$  is reduced only if the filtration rate is reduced; i.e., glucose reabsorption is not specifically impaired in hypertensive disease, and  $Tm_G$  is reduced only when the glomerulus of a nephron is obliterated by vascular changes and the attached tubule is passively cut off from reabsorptive activity. The alternative explanation, that specific impairment of tubular reabsorptive capacity is primary but that the filtration rate is simultaneously reduced to a proportional extent, so as

TABLE IV

*Glucose Tm and diodrast Tm in hypertensive subjects*

Each datum in columns 5, 6, 7, 8 and 9 represents the average of three or more clearance periods. Columns 5, 6, 7, 8 and 9 are corrected to 1.73 sq. m.; column 8 is corrected to 98.5°F.

SUBJECT	AGE	SUR- FACE AREA	DATE	PLASMA CLEARANCE		EFFECTIVE BLOOD FLOW	DIODRAST $T_m$	GLUCOSE $T_m$	INULIN CLEARANCE/ GLUCOSE $T_m$	DIODRAST CLEARANCE/ GLUCOSE $T_m$	GLUCOSE $T_m$ /DIODRAST $T_m$	INULIN CLEARANCE/ DIODRAST $T_m$	DIODRAST CLEARANCE/ DIODRAST $T_m$	FILTRATION FRACTION
				Inulin	Diodrast									
Men														
		sq. m.		cc. per minute	cc. per minute	cc. per minute	mg. iodine per minute	mg. per minute						
F. K.	21	1.64	3/13/39	121	604	1105	31.6	290	0.417	2.08	9.17	3.83	19.1	20.0
H. U.	47	1.70	3/29/39	114	544	899	26.5	255	0.447	2.13	9.61	4.30	20.5	20.9
U. B.	37	1.87	5/19/39	104	416	695	32.5	273	0.381	1.52	8.40	3.20	12.8	25.0
D. G.	48	1.82	10/25/40	136	567	1053	53.7	314	0.433	1.81	5.84	2.53	10.6	24.0
D. C.	58	1.97	11/ 3/40	105	530	888	25.7	308	0.341	1.72	11.98	4.08	20.6	19.8
S. K.	46	1.76	11/ 8/40	123	718	1116	43.3	410	0.300	1.75	9.46	2.84	16.9	17.1
R. La	66	1.74	11/11/40	112	500	910	32.6	331	0.338	1.51	10.15	3.43	15.3	22.4
S. W.	61	1.65	11/29/40	71	367	666	36.5	344	0.206	1.07	9.42	1.95	10.1	19.3
P. T.	60	1.76	1/24/41	62	280	470	24.9	322	0.192	0.87	12.92	2.49	11.2	22.1
A. C.	66	1.93	2/19/41	103	450	810		377	0.273	1.19				22.9
M. Gr	64	1.95	3/17/41	101	271	538	40.0	376	0.268	0.72	9.40	2.52	6.8	37.2
J. O.	43	1.94	3/12/41	80	347	691	30.5	197	0.406	1.76	6.46	2.62	11.4	23.1
A. B.	62	1.82	6/ 6/41	85	386	645	21.5	209	0.407	1.85	9.72	3.95	17.9	22.0
A. Bo	32	1.78	10/17/41	111	802	1710	57.0	280	0.396	2.86	4.91	1.95	14.1	13.9
M. S.	26	2.03	10/27/41	72	246	499	24.5	168	0.428	1.46	6.86	2.94	10.0	29.2
Women														
R. L.	49	1.29	3/10/39	145	570	976	32.6	381	0.381	1.50	11.68	4.44	17.5	25.4
L. J.	44	1.57	3/27/39	120	471	785	30.1	306	0.392	1.54	10.17	3.99	15.6	25.5
H. G.	34	1.73	4/19/39	63	207	362	12.3	162	0.389	1.28	13.17	5.12	16.8	30.4
M. Jo	37	1.62	5/ 1/39	114	556	785	38.6	276	0.413	2.01	7.15	2.95	14.4	20.1
M. A.	32	1.53	11/ 6/39	151	490	823	40.9	427	0.354	1.15	10.44	3.69	12.0	30.8
C. B.	55	1.60	2/21/41	141			33.2	446	0.316		13.43	4.25		
M. G.	41	1.85	2/17/41	140			44.7	385	0.363		8.61	3.13		
M. T.	34	1.54	3/ 3/41	127	579	984	35.1	316	0.402	1.83	9.00	3.62	16.5	22.0
J. M.	56	1.61	3/14/41	91	375	744	19.8	256	0.355	1.47	12.92	4.60	18.9	24.2
B. G.	40	1.64	10/15/41	89	485	840	34.7	242	0.368	2.00	6.98	2.56	14.0	18.3
A. H.	41	1.69	10/29/41	23	71	101	4.4	40	0.575	1.78	9.10	5.22	16.1	32.4
F. H.	49	1.60	10/31/41	10	34	47	2.3	12	0.833	2.83	5.22	4.35	14.8	29.4
B. S.	44	2.05	11/28/41	88	357	540	37.0	217	0.405	1.65	5.86	2.38	9.7	24.6
S. D.	60	1.56	12/19/41	45	216	437	16.0	129	0.349	1.67	8.06	2.81	13.5	20.8
A. M.	52	2.00	2/16/42	71	415	692	28.8	211	0.336	1.97	7.33	2.46	14.4	17.1

to maintain a normal  $C_{IX}/Tm_a$  ratio, seems less plausible since it requires a physiologically improbable coincidence.

The persistence of  $Tm_G$  when  $Tm_D$  is impaired is confirmatory evidence that our previous interpretation of the elevated  $C_{IN}/Tm_D$  ratio in hypertensive subjects is correct: namely, that nephrons which have in some measure lost the capacity to excrete diodrast are continuing to convey glomerular filtrate to the urine. Where, in particular subjects,  $C_{IN}/Tm_D$  is above normal,  $Tm_G/Tm_D$  is likewise above normal. Our choice of the term "impotent" to describe such non-excretory nephrons may be questioned since by the present demonstration they can still reabsorb glucose and probably other substances, but we think the term will continue to be useful until further data on specific functional attributes are available.

In résumé, in hypertensive disease the tubular excretory capacity for diodrast, as measured by  $Tm_D$ , is impaired, without an equal impairment in the reabsorptive capacity for glucose, as measured by  $Tm_G$ . In the earlier stages of the disease the filtration rate apparently is not affected, though ultimately arteriolar and capillary lesions do impair the filtration bed and in proportion as this is obliterated  $Tm_G$  is reduced below normal values simply because of glomerular destruction. In the terminal stages of the disease all functions may be reduced to vestigial levels.

The reduction in  $Tm_D$  appears to be the most characteristic impairment of renal function in essential hypertension, and the question arises as to the possible significance of this reduction in the etiology of the disease, especially since the evidence on man argues against the primacy of renal ischemia (6, 14, 17, 18, 20, 36, 40, 42). It is impossible to look upon the tubular excretion of such artificial compounds as diodrast and hippuran (iodohippuric acid) as interesting teleologic paradoxes. In unpublished observations we have found that the naturally occurring hippuric acid, phenylacetic acid and related compounds are excreted in a parallel manner (see 13) and we lean to the view that tubular excretion is a terminal step in a renal metabolic sequence, perhaps involving the conjugation of difficultly catabolizable aromatic residues such as benzoic and phenylacetic acids, and that a reduction in  $Tm_D$  may reflect a deficit in renal metabolic processes anterior to the process of excretion itself. In this connection increased interest attaches to the demonstration that  $Tm_D$  in dogs is reduced by hypophysectomy (47) and increased by large doses of testosterone (43) and vitamin A (Bing, unpublished observations) since by this evidence at least one process in renal metabolism is demonstrated to be related to factors outside the kidney. It remains to be discovered, however, whether the impairment of renal metabolism which is reflected in a reduction of  $Tm_D$  is causally related to the hypertensive process or whether the impairment is but one of the many degenerative effects of the disease.

#### V. THE TITRATION OF THE KIDNEYS WITH GLUCOSE AND DIODRAST

The examination of the kidneys by the simple determination of  $Tm_G$  and  $Tm_D$  is deficient for finer observations, in that it neglects the load of glucose or diodrast at which observations are made: the higher this load, the greater must be the decrease in glomerular filtration or tubular perfusion before a reabsorptive

or excretory unit will cease to contribute to the sum-total of tubular activity; while the load itself is dependent upon two terms, the plasma concentration of glucose or diodrast, as the case may be, and the volume of carrier, *i.e.*, glomerular filtrate or peritubular perfusion fluid. This deficiency can be circumvented by "titrating" the kidneys with glucose or diodrast: *i.e.*, by progressively raising the plasma concentration of these substances between critical physiologic levels, it is possible to saturate various reabsorptive or excretory "units" in inverse order to the relative volume of carrier which they receive, until all are saturated and definitive  $Tm_G$  or  $Tm_D$  is reached. From the titration curve so obtained the volume of carrier distributed to these various "units" can be stated in either relative or absolute terms.

The following section is devoted to the development of this titration method and its application to the normal and hypertensive kidney.

### 1. Glucose Titration

The following premises are erected:

(A) The phenomenon of a maximal glucose reabsorptive capacity, as observed in the overall activity of the two kidneys, reflects a similar quantitative limitation in every tubule: *i.e.*, every tubule reabsorbs all the glucose presented to it by its glomerulus until the load is exactly equal to its maximal reabsorptive capacity; when the load exceeds this capacity, the excess glucose is excreted in the urine.<sup>9</sup>

(B) The status of individual nephrons with respect to filtration rate and maximal glucose reabsorptive capacity remains unchanged during the period required for the completion of titration.<sup>10</sup>

Equation (1) (page 61), restated for individual nephrons in terms of the above premises, supplies the starting point for the following analysis. For individual nephrons (or functionally homogeneous categories of nephrons) the filtration rate may be indicated by  $c_{in}$ , the rate of glucose reabsorption by  $t$ , and the maximal reabsorptive capacity by  $tm$ .<sup>11</sup> Since a common stream of plasma supplies all glomeruli,  $p_g$  will be essentially identical for all nephrons and identical with  $P_g$ , the concentration of glucose in arterial plasma;  $c_{in}$  will, however, differ in various nephrons in consequence of differences in size and glomerular pressure; while  $tm$  will differ in various nephrons if for no other reason than be-

<sup>9</sup> It is here implied that there is negligible splay in the titration curve of any individual nephron, an implication supported by the relatively small splay in the titration curve of the entire kidneys, as shown in Figure 7.

<sup>10</sup> The necessity of maintaining the *status quo* throughout the process of titration is obvious and, since two to three hours are required to obtain a complete titration curve, the method in its present form is not adapted to the examination of the transient action of drugs, but is more suitable to the examination of the normal and diseased kidney under basal conditions, as applied here.

<sup>11</sup> The subscript  $g$  will be omitted from  $t_g$  and  $tm_g$ , but it is to be understood so long as we are dealing with glucose reabsorption, in order to differentiate these terms from the same terms used in Part V, section 3, for describing diodrast excretion.

cause the proximal segment<sup>12</sup> does not in all nephrons have the same size and length. In any particular nephron, the critical concentration of glucose required to just effect saturation of the tubule will vary directly as the maximal reabsorptive capacity of that tubule, and inversely as the rate of filtration in the glomerulus; so, generally, among a large number of nephrons those with the largest filtration rate per unit reabsorptive capacity, *i.e.*, the largest  $c_{in}/tm$  ratio, will saturate at the lowest level of  $P_G$ , while those with the lowest  $c_{in}/tm$  ratio will require the highest level of  $P_G$  to effect saturation. Only those nephrons in which the ratio  $c_{in}/tm$  is identical will saturate at the same value of  $P_G$ .

The ratio  $c_{in}/tm$  may be designated as "glomerular activity," and indicated by  $r$ , since it expresses the rate of filtration (cc. per min.) in the glomerulus of a particular nephron, relative to the quantity of reabsorptive tissue in the tubule of that nephron, as measured by the maximal rate of glucose reabsorption (mg. per min.).<sup>13</sup>

We may speak of all nephrons which have, within practical limits of determination, the same  $c_{in}/tm$  ratio, as belonging to a "category" in respect to glomerular activity. The various nephrons in a "category" may have different absolute values of  $c_{in}$  or  $tm$ ; these absolute values cannot be determined by the titration method, which reveals only differences in the ratio of these terms.

The following terms are used in the mathematical analysis of the titration curve:

$T_G$  = Total tubular reabsorption of glucose (mg. per min.).

$Tm_G$  = Maximal value of  $T_G$ .

$P_G$  = Plasma concentration of glucose (mg. per cc.).

$C_{IN}$  = Glomerular filtration rate (cc. per min.).<sup>14</sup>

$U_GV$  = Rate of excretion of glucose (mg. per min.).

The next five terms are applicable in principle either to a unit of reabsorptive tissue (*i.e.*, a single nephron), or to an experimentally measured category of units having the same glomerular activity.

$c_{in}$  = Rate of filtration in an unsaturated nephron (cc. per min.).

$\bar{c}_{in}$  = Rate of filtration in a saturated nephron (cc. per min.).

$t$  = Rate of glucose reabsorption in an unsaturated nephron (mgm. per min.).

<sup>12</sup> It is demonstrated by the recent work of Walker, Bott, Oliver and MacDowell (41) on the mammalian nephron, that the reabsorption of glucose is a function of the proximal tubule.

<sup>13</sup> The reader will note that any reference to glomerular activity implies one or another standard of reference, such as the filtration rate in cc. per single glomerulus, or per unit of glomerular volume, diameter or area of filtering surface, etc. The present method of examination functionally relates the *volume* of glomerular filtrate to the *maximal glucose reabsorptive capacity* of the attached nephron.

<sup>14</sup> The term  $C_{IN}$  is usefully established for describing the filtration rate and is used in all equations here even though in much of the work mannitol was substituted for inulin. Wherever mannitol was used the fact is either stated in the text or the filtration rate is described as the mannitol clearance,  $C_M$ , in the legend.

$tm$  = Rate of glucose reabsorption in a saturated nephron (mgm. per min.).

$r$  = Glomerular activity ( $c_{in}/tm$ ) in a particular nephron.

$tm$   $Tm_g$  = Size of a category having a particular glomerular activity, expressed as a fraction of the entire tubular reabsorptive mass.

$R$  = Total glomerular activity ( $C_{IN}/Tm_g$ ) in the entire kidneys (which is also equal to the *mean* value of  $c_{in}/tm$ ).

$R_{normal}$  = Average value of mean glomerular activity in normal subjects.

Let it be supposed that  $P_g$  has been progressively raised from low levels, where no nephrons are saturated, to a level  $P_{g'}$ , at which an appreciable number of nephrons having a high glomerular activity are just saturated. The kidney is now nominally divided into two portions, one portion,  $a$ , in which all the nephrons are saturated, and a residuum,  $b$ , in which no nephron is saturated. For the portion,  $a$ ,

$$(3) \quad P_{g'} \Sigma c_{in} = \Sigma tm$$

where  $\Sigma c_{in}$  and  $\Sigma tm$  are, respectively, equal to the sum of  $c_{in}$  and  $tm$  in all nephrons considered as saturating at  $P_{g'}$ .

Now let  $P_g$  be raised to  $P_{g''}$ , a value sufficiently high to cause the nephrons in  $a$  to excrete a measurable quantity of glucose, but not high enough to saturate any nephrons in  $b$ . At  $P_{g''}$ , all the glucose filtered in  $a$  in excess of  $\Sigma tm$  will appear in the urine; and, since no glucose will be excreted by the unsaturated nephrons in  $b$ , the increment in glucose excretion ( $\Delta U_g V$ ) will be equal to  $(P_{g''} - P_{g'}) \Sigma c_{in}$ . Writing  $(P_{g''} - P_{g'}) = \Delta P_g$ ,

$$(4) \quad \Sigma c_{in} = \frac{\Delta U_g V}{\Delta P_g}$$

The total filtration rate,  $C_{IN}$ , is the sum of the filtration rate in the saturated portion,  $\Delta C_{in}$ , plus that in the unsaturated portion,  $\Sigma C_{in}^-$ :

$$(5) \quad C_{IN} = \Sigma c_{in} + \Sigma c_{in}^-$$

The total rate of glucose reabsorption,  $T_g$ , is the sum of the rate of reabsorption in the saturated portion,  $\Sigma tm$ , and in the unsaturated portion,  $\Sigma t$ :

$$(6) \quad T_g = \Sigma tm + \Sigma t$$

$\Sigma t$  is the rate of glucose filtration in the unsaturated portion:

$$(7) \quad \Sigma t = P_{g'} \Sigma c_{in}^- = P_{g'} (C_{IN} - \Sigma c_{in})$$

Hence from (4) and (6)

$$(8) \quad \Sigma tm = T_g - P_{g'} \left( C_{IN} - \frac{\Delta U_g V}{\Delta P_g} \right)$$

Since  $C_{IN}$  and  $Tm_g$  differ in various subjects, it is convenient for graphical comparison to express the titration curve in the universal terms of  $T_g/Tm_g$

and  $P_g C_{IN}/Tm_g$ , as in all the Figures in this paper: to which end we may write  $\Sigma c_{in} = \frac{\Delta T_g}{\Delta P_g}$ , and, by rearrangement of (5) and conversion to units of  $C_{IN}$  and  $Tm_g$ ,

$$(9) \quad \frac{\Sigma c_{in}}{C_{IN}} = 1 - \frac{\Delta T_g/Tm_g}{\Delta P_g C_{IN}/Tm_g}$$

or by rearrangement of (8)

$$(10) \quad \frac{\Sigma tm}{Tm_g} = \frac{T_{g'}}{Tm_g} - P_{g'} C_{IN}/Tm_g \frac{\Delta T_g/Tm_g}{\Delta P_g C_{IN}/Tm_g}$$

where  $T_{g'}$  and  $P_{g'}$  are simultaneous values, and  $\Delta T_g$  and  $\Delta P_g$  are corresponding increments between  $P_{g'}$  and  $P_{g''}$ .

By applying (9) and (10) at progressively higher values of  $P_g$ , the values of  $\Sigma c_{in}$  and  $\Sigma tm$  are calculated for an ever-increasingly large saturated portion of the kidney; the successive *increments* in these terms, which may be designated simply as  $c_{in}$  and  $tm$ , represent the absolute rates of filtration and the absolute quantity of tubular tissue in successive categories saturating at progressively higher values of  $P_g$ . Hence  $c_{in}/C_{IN}$  and  $tm/Tm$  expresses these terms as relative fractions of the total filtration rate or excretory capacity.

It is not only cumbersome to describe the glomerular activity,  $r$ , of various categories in absolute units (cc./mg./min.) but less illuminating than when this glomerular activity is expressed relative to  $r_{mean}$  for the kidneys as a whole. But  $r_{mean}$  is identical with  $\Sigma c_{in}/\Sigma tm$ , which in turn is identical with  $C_{IN}/Tm_g$ . Hence for any category which just saturates at  $P_{g'}$ ,  $P_{g'} c_{in} = tm$ , and

$$(11) \quad r/R = \frac{c_{in}/tm}{C_{IN}/Tm_g} = \frac{1}{P_{g'} C_{IN}/Tm_g}$$

The above ratio,  $r/R$  can be called the relative glomerular activity of a particular category.

In the work book the calculations are carried through from  $P_g$ ,  $U_g$  and  $V$ , by means of (1), to the terms appearing in (9) and (10), the corresponding values of the titration curve being then plotted as in our Figures. Since  $U_g V$  is determined from urine samples which of necessity are collected over relatively long periods of time, the titration curve<sup>15</sup> is broken into a relatively few linear seg-

<sup>15</sup> Any increase in  $P_g$  beyond the level required to saturate those nephrons having the highest glomerular activity can only be accompanied by either (a) saturation of nephrons having a lower glomerular activity, or (b) spilling of all filtered glucose in excess of the reabsorptive capacity of all available nephrons. In (a),  $\Delta U_g V/\Delta P_g$  will necessarily increase as  $P_g$  is raised, approaching the maximal ratio of 1.0, which will obtain in (b). Since an increase in  $\Delta U_g V/\Delta P_g$  requires a corresponding decrease in  $\Delta T_g/\Delta P_g$  the titration curve relating  $T_g$  to  $P_g$  (or to  $P_g C_{IN}/Tm_g$ ) will always be concave to the abscissae. That is, a kidney in which the dispersion of glomerular activity is constant throughout titration cannot yield a convex or sigmoid titration curve, and the presence of convexity implies a change in glomerular activity.

ments, the size of each segment being proportional to  $\Delta U_g V$ ; i.e., in effect the kidneys are broken up into a small number of large categories. It has been our practice to collect 12 to 15 urine periods, and to draw a smooth titration curve through the resulting observations. Any point along this curve may be chosen arbitrarily as corresponding to the point of saturation of a category, the relative glomerular activity ( $r/R$ ) of which is given by equation (11); it is then an equally arbitrary election whether the size of this category is to be expressed as a fraction of the total filtration rate ( $c_{in}/C_{IN}$ ) or as a fraction of the total reabsorptive tissue ( $tm/Tm_g$ ), but since  $Tm_g$  is presumably a constant in any one individual, the latter method of expression is preferable. Hence in practice only equation (10) is used in conjunction with (11).

## 2. The frequency distribution curve

A frequency distribution curve conventionally presents the number of individuals, or the per cent of the total population, in each of several "categories" of the "variable" under examination, where each category represents the *same increment* in this variable. If the dimensions of various categories were different, this circumstance would of course affect the relative number of individuals falling within them and the frequency distribution curve would lose its definitive meaning.

In the present problem the "variable" under examination is the relative glomerular activity,  $r/R$ , and it is required that the frequency distribution curve describe categories each of which represents the same increment ( $\Delta r/R$ ) in this term. The minimal size of this increment could in principle be as small as the minimal difference between any two nephrons, but of course in practice experimental error precludes any such refinement and the minimal category size must be chosen arbitrarily. It must, moreover, be of the same size in all frequency distribution curves which are to be compared with each other. To this end we have chosen for the category dimension,  $\Delta r/R$ , the value 0.1, or 10 per cent of  $r_{\text{mean}}/R$ , the latter ratio of course having a value of 1.0 since these two terms are arithmetically identical.

Having determined from the titration curve the extreme lower (or upper) limit of  $r/R$ , values of  $r/R$  above (or below) the value are set down, each differing from its predecessor by 0.1;  $P_D \cdot C_{IN}/Tm_g$  is then calculated as  $R/r$ , the corresponding value of  $T_g/Tm_g$  is read off from the smoothed titration curve, and  $tm/Tm_g$  is calculated by difference after the application of (10). Very slight differences in the slope of the titration curve result in marked differences in  $tm/Tm_g$  and consequently the resulting frequency distribution curve must be smoothed and interpreted with due consideration of this fact.

Since the frequency distribution curve for a particular subject, when expressed as above, shows only the distribution of glomerular activity relative to the subject's mean value,  $R$ , it fails to show whether  $R$  itself is above or below normal; for this purpose it is convenient to append a secondary scale,  $r/R_{\text{normal}}$ , so placed below  $r/R$  that there is coincidence between the zero ordinates of the two scales, and also between the ordinates  $r/R = 1.0$  and  $R/R_{\text{normal}}$ , the values

of  $R_{\text{normal}}$  for men and women being given in Table III. The two scales thus give at a glance both the relative and absolute glomerular activity throughout the kidneys. For illustration the reader is referred to Figure 9, etc.

### 3. Diodrast titration

The above principles are directly applicable to the determination of the relative perfusion rate of tubular tissue. Again the central fact is the circumstance that this tissue is characterized by a maximal capacity for the excretion of diodrast, which under premises *A* and *B* (page 78), and starting from equation (2) (page 62), may be translated into terms of individual excretory units, or categories of such units.

The following symbols are used:

$T_D$  = Total tubular excretion of diodrast iodine (mg. per min.).

$T_{m_D}$  = Maximal value of  $T_D$ .

$P_D$  = Plasma concentration of diodrast iodine (mg. per cc.).

$C_{IN}$  = Glomerular filtration rate (cc. per min.).

$U_D V$  = Rate of excretion of diodrast iodine (mg. per min.).

$F$  = Per cent free diodrast in plasma (see nomogram in reference 38).

$W$  = Per cent protein-free water in plasma/100 (FW is taken as 0.73 in most calculations).

$C_D$  = Plasma diodrast clearance or  $U_D V / P_D$ .

$V_e$  = Rate of perfusion of entire tubular excretory tissue.

$E_p$  = Overall (arterial-venous) extraction ratio of diodrast.

$\bar{E}$  = Mean plasma extraction ratio of diodrast from plasma perfusing unsaturated tubular excretory tissue.

$E$  = Plasma extraction ratio just at point of saturation.<sup>16</sup>

The next five terms are applicable in principle to a unit of tubular excretory tissue (tubule cell), or to an experimentally measured category of units having the same perfusion rate.

$\bar{v}_o$  = Rate of perfusion of unsaturated tubular excretory tissue.

$v_o$  = Rate of perfusion of saturated tubular excretory tissue.

$t$  = Rate of diodrast iodine excretion in unsaturated tubular excretory tissue (mg. per min.).

$tm$  = Rate of diodrast iodine excretion in saturated tubular excretory tissue (mg. per min.).

$r$  = Tubular perfusion rate ( $v_o/tm$ ) in a particular unit of tubular excretory tissue.

$tm/T_{m_D}$  = Size of a category having a particular perfusion rate, expressed as a fraction of the entire kidneys.

$R$  = Tubular perfusion rate ( $V_o/T_{m_D}$ ) of the entire kidneys.

$R_{\text{normal}}$  = Average value of mean perfusion rate in normal subjects.

Two important differences between glucose and diodrast titration concern the determination of the volume of carrier.

<sup>16</sup>  $\bar{E}$  and  $E$  are to be distinguished from  $E_p$ , the overall plasma extraction ratio, which is lower than either  $\bar{E}$  or  $E$  in consequence of blood perfusing inert tissue.

First, during glucose titration, the total volume of carrier (glomerular filtrate) can be measured throughout the titration process. During diodrast titration, however, the elevation of the plasma diodrast concentration, by saturating some excretory units, lowers the overall extraction ratio of diodrast so that the excretion of this substance is no longer an index of renal plasma flow. Consequently the renal plasma flow must be measured at low plasma levels of diodrast prior to the elevation of the latter for titration purposes, and it must be assumed that this control figure will be applicable throughout the titration process—*i.e.*, that the renal plasma flow will remain constant.

Second, during glucose titration, all the glomerular filtrate must be conceived as carrying glucose to the tubules. During diodrast titration, however, the effective volume of carrier must be equated with that nominal fraction of the plasma diodrast which is delivered to the parietal surface of the tubules—excluding the fraction which is filtered off by glomerular filtration—for only this fraction is available to be excreted by the tubular tissue or to participate in its saturation. The volume of plasma which is in effect diverted by filtration is  $FWC_{IN}$ , as in equation (2).<sup>17</sup> The volume of plasma which remains to perfuse the tubules may be calculated from the diodrast clearance,  $C_D$ , and the plasma extraction ratio,  $\bar{E}$ , of the tubular perfusate. The total rate of diodrast excretion,  $U_D V$ , is the sum of the diodrast excreted by filtration, or  $P_D FWC_{IN}$ , and that excreted by the tubules; at low values of  $P_D$  the latter term is equal to  $V_o$ , the volume of plasma perfusing the tubules, multiplied by  $\bar{E}$ , the extraction ratio across unsaturated tubules, and the plasma concentration,  $P_D$ :

$$(12) \quad U_D V = P_D V_o \bar{E} + P_D FWC_{IN}$$

Dividing by  $P_D$

$$(13) \quad C_D = V_o \bar{E} + FWC_{IN}$$

Hence the volume of tubular perfusate is

$$(14) \quad V_o = (C_D - FWC_{IN})/\bar{E}$$

and the load of diodrast carried to the tubules by this perfusate is

$$(15) \quad P_D V_o = P_D (C_D - FWC_{IN})/\bar{E}$$

In equation (15)  $\bar{E}$  is unknown, and not determinable even by means of simultaneous arterial and venous renal blood, for it refers specifically to blood perfusing active excretory tubular units, to the exclusion of blood perfusing inert

<sup>17</sup> It is immaterial whether the filtered diodrast is actually removed from plasma which subsequently passes to tubular tissue, or from plasma which never reaches tubular tissue; in the calculation of  $C_D$  all excreted diodrast is included, and whatever is excreted by filtration must be deducted in calculating tubular load. Insofar as the red cells carry diodrast, they will contribute to  $U_D V$  and increase the apparent plasma clearance, but where the fraction of diodrast carried by the red cells remains constant at all plasma levels the resulting error will not influence the form of the titration curve. However, recent studies lead us to believe that red cell transport in man is negligible and the point may be neglected here.

tissue such as the fibrous and fatty capsule, connective tissue and non-excretory portions of the tubules. However, the overall extraction ratio,  $E_p$ , in the explanted kidney of the dog averages in the data of White (46) 0.75, and in those of Corcoran, Smith and Page (11), 0.85; since  $\bar{E}$  refers only to the blood presented to active tubular tissue it is our belief that it is substantially above 0.90, and for our present purposes may be taken as 1.0. In which case  $V_o$  can be calculated from the other clinically measurable terms of (14).

In the diodrast titration it must be recognized that one tubule cell is presumably the anatomical unit of "saturation" (unlike glucose titration where an entire nephron must presumably be saturated before any of the filtered glucose delivered to that nephron will be excreted in the urine); and it must be assumed, as in premise A, that each cell will continue to excrete all diodrast delivered to it until saturation occurs—*i.e.*, that there is no intrinsic splay in the cellular excretory mechanism.<sup>18</sup> This assumption is warranted by the narrow splay in the titration curve of the entire kidney, as shown in Figure 7.

Equations (16) to (24) which follow, are parallel to equations (3) to (11), except for the substitution of tubular excretion ( $T_D$ ) for tubular reabsorption ( $T_G$ ).

Let the plasma diodrast concentration,  $P_D$ , be raised to a level  $P_{D'}$ , at which an appreciable quantity of tubular tissue is just saturated; then

$$(16) \quad EP_{D'}\Sigma v_o = \Sigma tm$$

where  $\Sigma v_o$  is the total rate of perfusion of the saturated tissue, and  $\Sigma tm$  is the total quantity of tubular tissue in the saturated portion, while  $E$  is the extraction ratio of diodrast in the perfusion  $v_o$  at  $P_{D'}$ .<sup>19</sup> Here  $\Sigma v_o$  is conceived as expressing the virtual flow per minute of a fluid having the same concentration of diodrast as the post glomerular plasma.

<sup>18</sup> This is not true, apparently, of phenol red, but it does appear to be true of diodrast since the normal titration curve, as shown in Figure 7, is a relatively sharp angle. If saturation did not occur until the excretory tissue were presented with an excess load, this circumstance would give the appearance of a splay in the titration curve. Were such a splay present, the question would have to be answered whether it is attributable to lack of uniformity in perfusion rate, or to an inherent characteristic of tubular kinetics; but since an appreciable splay is normally absent, the question has little importance for the normal kidney. Where splay does appear, as in J. G. and E. F. (fig. 8) it must be a result of a disproportion in either the numerator or denominator of the ratio,  $v_o/tm$ ; if attributed to the latter, it might be attributed to a change in the intrinsic behavior of each excretory unit, but the argument has little importance when one is dealing not only with two million odd nephrons, but with many times this number of excretory cells; *i.e.*, the units of excretion are so small and so numerous that for nearly all purposes we may consider them as quantitatively fixed in excretory capacity. Partial loss of capacity in individual cells in consequence of some pathological process would be equivalent, so far as the titration method is concerned, to a reduction in cell size, and we cannot *apriori* suppose that all cells normally have exactly the same excretory capacity.

<sup>19</sup> We have elsewhere (35) pointed out that diodrast molecules not available for clearance at low plasma concentrations ( $C_D$ ) will not in all probability be made available for tubular saturation ( $Tm_D$ ) merely in consequence of increasing the plasma diodrast concentration. Hence  $E$  may be taken as equal  $\bar{E}$ , which we take equal to 1.0.

Now let  $P_{D'}$  be raised to  $P_{D''}$ , a level sufficiently high to cause the tubular tissue in the unsaturated portion to excrete a measurably increased quantity of diodrast, but not high enough to saturate any additional tissue. For all unsaturated tissue (writing  $P_{D''} - P_{D'} = \Delta P_D$ ),

$$(17) \quad \Sigma \bar{v}_0 = \frac{\Delta T_D}{\Delta P_D \bar{E}}$$

where  $\Sigma \bar{v}_0$  is the total perfusion rate of the unsaturated tissue,  $\Delta T_D$  is the increment in total tubular excretion and  $\bar{E}$  is the extraction ratio of the diodrast in the perfusate going to this unsaturated tissue.

The total volume of plasma,  $V_o$ , perfusing all tubular tissue is equal to the sum of that perfusing the saturated portion,  $\Sigma \bar{v}_o$ , and that perfusing the unsaturated portion,  $\Sigma \bar{v}_0$ :

$$(18) \quad V_o = \Sigma \bar{v}_o + \Sigma \bar{v}_0$$

The total tubular excretion of diodrast is equal to the sum of diodrast excreted by the saturated portion,  $\Sigma tm$ , and the unsaturated portion,  $\Sigma t$ :

$$(19) \quad T_D = \Sigma tm + \Sigma t$$

The rate of excretion by the unsaturated portion is

$$(20) \quad \Sigma t = P_{D'} \Sigma \bar{v}_0 \bar{E}$$

From (17), (19) and (20),

$$(21) \quad \Sigma tm = T_D - P_{D'} \frac{\Delta T_D}{\Delta P_D}$$

where  $T_D$  and  $P_D$  are simultaneous values, and  $P_{D'}$  is the lower value of  $\Delta P_D$ .  $\bar{E}$  has cancelled out since both (17) and (20) refer to the same unsaturated nephrons.

To collate different individuals in terms of  $T_D/Tm_D$  and  $P_D V_o/Tm$ , we may substitute (17) in (18) and convert to units of  $V_o$  and  $Tm_D$ :

$$(22) \quad \frac{\Sigma \bar{v}_0}{V_o} = 1 - \frac{\Delta T_D/Tm_D}{\bar{E} \Delta P_D V_o/Tm_D}$$

Introducing the same units into (21):

$$(23) \quad \frac{tm}{Tm_D} = \frac{T_{D'}}{Tm_D} - \frac{P_{D'} V_o \Delta T_D/Tm_D}{Tm_D \Delta P_D V_o/Tm_D}$$

Since in any category which just saturates at  $P_{D'}$ ,  $EP_{D'} v_0 = tm$ , it follows that  $r = 1/EP_{D'}$ . Dividing both sides by  $V_o/Tm_D$

$$(24) \quad \frac{r}{\bar{R}} = \frac{v_0/tm}{V_o/Tm_D} = \frac{1}{EP_{D'} V_o/Tm_D}$$

Here  $V_o = (C_D - FWC_{IX})/\bar{E}$  (equation 14), and substitution leads to the term  $E/\bar{E}$ , where  $E$  is the diodrast extraction ratio in the plasma perfusing a particu-

lar category just at saturation, and  $\bar{E}$  the extraction ratio of diodrast from the entire tubular perfusate at low plasma levels (whence  $V_o$  is determined). Since  $\bar{E}$  is certainly above 0.90 and probably close to 1.0 (see footnote 19), the ratio  $E/\bar{E}$  may for practical purposes be taken as unity, whence

$$(25) \quad \frac{r}{\bar{R}} = \frac{1}{P_D(C_D - FWC_{IN})/Tm_D}$$

where all the terms are clinically determinable. In all calculations here  $V_o$  is taken as equal to  $C_D - FWC_{IN}$ . Equation (25) yields the relative tubular perfusion, or the tubular perfusion of a category expressed relative to the mean tubular perfusion of the entire kidneys as unity.

In the working equations (22), (23) and (25), the definitive value of  $Tm_D$  is presumed to have been determined independently of the titration process. Since  $Tm_D$  rather than  $V_o$  is the fixed physiological term,  $tm/Tm_D$  (equation 23) rather than  $v_o/V_o$  (equation 22) has been chosen to designate units of renal tissue the perfusion rate of which is under examination, and the values of  $tm/Tm_D$  are calculated as the differences between the successive values of  $\Sigma tm/Tm_D$  obtained by application of (equation 23) to progressively higher values of  $T_D$  interpolated in the smoothed titration curve at selected values of  $P_D$ . The latter are selected at intervals of  $r/R = 0.1$ , beginning at either end of the titration curve, for the reasons stated in the discussion of glomerular activity.

#### 4. Theoretical implications of the titration methods

In order to visualize the application of the titration methods, we have presented in Figure 5 three symmetrical frequency distribution curves applicable to either  $c_{in}/tm$  or  $v_o/tm$ , and the corresponding titration curves.<sup>20</sup> For a discussion of the statistical characteristics of these curves the reader is referred to the accompanying legend.

In considering the limits of dispersion in glomerular activity and tubular perfusion which might, on a statistical basis alone, be expected in the normal kidney, it may be noted that the standard deviation ( $\sigma$ ) among various physiological variables usually ranges from 14 to 20 per cent of the mean. It will be recalled that the standard deviation expressed in per cent of the mean ( $100\sigma/m$ ) is called the coefficient of variation. An interesting list of coefficients of variation for various physiological variables is given by Pearl (25);  $100\sigma/m$  is less than 14 per cent chiefly in anatomically rigid characters, such as body and bone measurements, while it is greater than 20 per cent in clinically unselected or

<sup>20</sup> In calculating the titration curve corresponding to a given frequency distribution curve, the range of  $r/R$  must be fitted to the configuration of the curve in such a manner that the mean value of  $v_o/tm$  divided by the mean value of  $r/R$  shall equal  $V_o/Tm$ ; that is, the condition must be fulfilled that for the category which stands at the center of gravity of the curve,  $v_o/tm = V_o/Tm$ . This is most easily accomplished by a process of approximation, starting by setting  $r/R = 1.0$  opposite  $\Sigma tm/Tm = 0.5$ , and raising or lowering  $r/R$  if  $\Sigma v_o$  is less or greater than 1.0, until  $\Sigma v_o = 1.0$ , when  $\Sigma tm/Tm = 1.0$ . In this reverse calculation,  $r/R \times tm/Tm = v_o/V_o$ ; if  $Tm$  is taken as equal to 1.0,  $T = \Sigma tm + P(1 - \Sigma v_o/V_o)$ , where  $P = R/r$ .

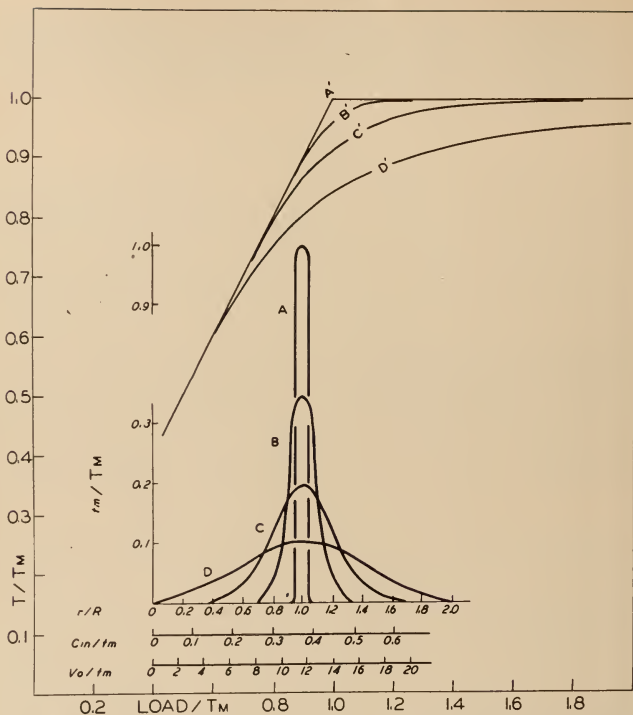


FIG. 5. Symmetrical frequency distribution curves and corresponding titration curves.

The curves are equally applicable to the distribution of glomerular activity or tubular perfusion, and are discussed as though  $r/R$  may be read in either sense. The curves are constructed to illustrate the following conditions:

A. Where  $r/R$  is identical for all nephrons. Here all nephrons will saturate at a load/ $T_m$  ratio = 1.0, and the titration curve will follow the abrupt angle,  $A'$ .

B. Where  $r/R$  is distributed in conformity with the "normal" frequency distribution curve, the dispersion being such that 95.4 per cent of the nephrons fall within the range of 0.80 to 1.20 times the mean. The titration curve,  $B'$ , departs from the sharp angle  $A'$  so little that the deviation is practically undetectable.

C. A "normal" frequency distribution, with the dispersion such that only 68.3 per cent of the nephrons fall within the range of 0.80 to 1.20 times the mean, 95.4 per cent falling within the range of 0.60 to 1.40 times the mean. The titration curve,  $C'$ , deviates from  $A'$  to an extent which is, from the technical point of view, generally determinable in the ease of  $c_{in}/t_m$ , and determinable under favorable conditions in the case of  $v_o/t_m$ .

With this degree of dispersion  $\sigma$  has a value of 20 per cent of the mean, and in the text reasons have been given for presuming that this degree of dispersion is of the order to be expected in physiological variables such as glomerular activity and tubular perfusion.

D. The dispersion of  $r/R$  is maximally increased. Since  $r/R$  must approach zero as a lower limit, symmetry requires that the upper limit approach 2.0. The titration curve,  $D'$ ,

definitely pathological organ weights where extreme variations are to be anticipated, or in psychodependent characters such as rapidity and steadiness of hand, visual acuity and dermal sensitivity. It lies between 15 and 20 per cent in most counterbalanced or regulated physiological functions, such as pulse rate, respiratory rate, vital capacity, reaction time, auditory acuity, normal liver, heart and kidney weights, and the like. It may also be noted that in different subjects various features of renal function have values for  $100\sigma/m$  ranging from 13 to 20 per cent, as shown in Table III. It cannot of course be argued that the dispersion of a variable in different subjects bears directly on the dispersion of the same variable between nephrons in any one subject, yet where two counterbalanced functions are involved, as in  $c_{in}/tm$  and  $v_o/tm$ , we may reasonably anticipate the same order of magnitude of dispersion.

In curve  $C$  of Figure 5,  $100\sigma/m$  is assigned a value of 20 per cent; since the curve is given a "normal" frequency distribution, it follows that 68.3 per cent of

begins to splay when  $load/Tm = 0.5$  (which in relation to saturation corresponds to  $r/R = 2.0$ ) and rises towards  $Tm$  as an asymptote which is reached only when  $load/Tm = \infty$  (corresponding to  $r/R = 0.0$ ).

*Deformation resulting from independent variation.* The so-called "normal" frequency distribution curves shown above are derived by aid of probability theory, the curve being calculated by means of the binomial equation  $(p + q)^n$ , where  $p + q = 1$ , and  $p = q$  (i.e.,  $p = 0.5$  and  $q = 0.5$ ). Where deformation of this curve is attributable to circumstances which may act on the value of  $r/R$  in one nephron independently of any other nephron—i.e., where variation of any one nephron ( $p$ ) is independent of variation in any other ( $q$ )—the resulting skewed curve will still be described by the equation  $(p + q)^n$  where  $p + q = 1$ , but  $q$  will no longer be equal to  $p$ . Setting  $q$  at very small values and taking  $n$  at appropriately large values leads to unimodal curves resembling  $v_o/tm$  in Figures 8 and 10. Moderate deformation by 'independent variation' leads to curves so slightly skewed that in the titration curve the observations remain close within the angle,  $A'$ , and are not distinguishable in practice from such a curve as  $B'$ . Deformation by 'independent variation' appears to be characteristic of tubular perfusion in the cases of essential hypertension studied here.

*Deformation arising otherwise than by independent variation.* Where variation in one nephron is not independent of variation in others, but where certain nephrons are affected because others are affected or where large numbers are necessarily affected simultaneously, and where the circumstances giving rise to variation are unknown, the course of deformation of the distribution curve cannot be predicted. In principle, the frequency distribution curve could take an infinite variety of shapes. Two general trends might, however, be expected: a shift in population towards low (or high) categories could occur in such a manner as to produce a unimodal curve skewed to right or left, in the general manner of 'independent variation' curves where  $p > q$  (resembling  $v_o/tm$ , fig. 10); or the population may become divided into two or more groups—one severely affected and the other unaffected—leading to the production of distribution curves with two or more modes (such as  $c_{in}/tm$  in figs. 10, 11, etc.). Deformation indicative of variation of the latter type is particularly evident in glomerular activity distribution curves in our subjects with essential hypertension.

*Reference to mean normal values.* The reader will note that since the ratio,  $r/R$ , has been taken as the essential physiological variable in defining our frequency distribution curve, all such curves for different individuals are strictly comparable, both in respect to total area and to the mean, or center of gravity (where  $r/R = 1.0$ ). The advantages of this method of presentation are obvious, but these advantages are in some measure offset by the consequence that the absolute values of  $r$  (i.e., of  $c_{in}/tm$  and  $v_o/tm$ ) are lost by reference to the mean ( $R$ ), and hence there is available no information on whether the mean is above or below the normal mean. It is therefore convenient to append a second scale in which  $r/R_{normal}$  is set in apposition to  $r/R = 1.0$ . This has been done in all subsequent Figures, but in the present Figure this would amount to mere duplication since  $R = R_{normal}$ ; consequently the secondary scale has here been made to read in *absolute units* by setting in apposition to  $r/R = 1.0$  the absolute mean normal values for men ( $C_{IX}/Tm_G = 0.371$  and  $V_o/Tm_D = 11.6$ ). For women,  $C_{IX}/Tm_G = 0.395$  and  $V_o/Tm_D = 11.9$ . The values for  $C_{IX}/Tm_G$  are taken from Table III (combined series).  $V_o/Tm_D$  is calculated as  $(C_D - 0.73 C_{IX})/Tm_D$ , using the respective male and female mean normal values for these terms as given in the above Table.

the observations will fall within the range of  $m \pm \sigma$ . Assuming that  $c_{in}/tm$  or  $v_o/tm$  is symmetrically distributed in accordance with the normal frequency distribution, curve  $C$  would then represent the anticipated distribution curve, and  $C'$  the corresponding titration curve, for either glomerular activity or tubular perfusion.

### 5. Sources of error and permissible corrections

It is frequently difficult to obtain complete emptying of the bladder, even with 20 cc. of washout fluid, and this source of error, coupled with errors in timing the end of successive collection periods, may lead to a rough, alternate staggering in the titration curve. Where such errors are present they are generally revealed by the alternation of low and high values for the filtration rate, and it seems permissible to correct for them by correcting the urine volume in such a manner as to yield for the two successive periods a constant filtration rate equal to the mean value of the two periods. The correction, however, should not be extended beyond two successive periods unless it is evident that the filtration rate has remained constant for a longer period of time.

Wherever  $P_g$  or  $P_d$  are changing significantly, two and a half minutes should be deducted for "delay time" elapsed between the sampling of blood and the appearance in the bladder of urine formed from this blood (8, 37).

Since the titration curve is a smoothed curve, and the frequency distribution curve is further smoothed between the calculated values of  $tm/Tm_G$  or  $tm/Tm_D$ , the latter is not to be given more weight than is warranted by the overall contours of either.

The discovery of glomeruli of relatively low activity is practically difficult since it depends upon minute changes in  $U_gV$  at a time when  $P_g$  is relatively large, and when small errors in  $P_g$  or in  $C_{IN}$  produce large errors in the calculation of  $T_g$ . But the discovery of glomeruli of relatively high activity is comparatively simple, since they will saturate at relatively low values of  $P_g$  and hence their presence will be revealed by the appearance of glucose in the urine at  $P_gC_{IN}/Tm_g$  ratios lower than 1.0. The normal excretion of total reducing substances, which ranges from 0.5 to 2.0 mg. per minute, is quite constant in any one subject in successive clearance periods and serves as a satisfactory base line from which to detect increased glucose excretion. An increment in  $U_gV$  of 2.5 mg. per minute above the basal excretion of total reducing substances is well within practical determination. This represents less than one per cent of the total reabsorptive capacity of the kidney, and by appropriate adjustment of  $P_g$ , saturation of this fraction of tubular tissue is in principle detectable.

$Tm_g$  must frequently be estimated at  $P_gC_{IN}/T_g$  ratios less than 2.0, and where there are significant numbers of nephrons having a relative glomerular activity less than 0.5, this fact may lead to an error in  $Tm_g$  measurement. If  $Tm_g$  is taken at too small a value, this error tends to decrease the splay in the titration curve and to deform the distribution curve by narrowing the limits of dispersion. In the net, however, a titration curve is obtained which describes the distribution of glomerular activity in those glomeruli the tubules of which are accessible

to glucose saturation, and this distribution will probably not differ greatly in most instances from the distribution with all nephrons taken into account.

It has been noted that in diodrast titration the volume of carrier to the tubules,  $V_o$ , must be determined independently of the titration process, and preferably just before titration is begun. It is then assumed that the renal plasma flow remains constant during titration. We believe that with the proper precautions this condition will generally be fulfilled, but it is obviously the major weakness of the diodrast titration method. Exceptions are noted in the discussion of individual subjects in the following section.

The discovery of tubules of relatively high perfusion rate is rendered the more difficult by possible changes in total tubular perfusion, a decrease in the latter giving the effect of a depression of  $T_D$  in consequence of tubular saturation; hence the titration should be carried out under conditions favoring a stable renal blood flow. In curve  $D$ , for example, saturation of the first tubular tissue would occur at  $P_D V_o / Tm_D = 0.5$ , but since  $V_o / Tm_D$  rarely exceeds 20, this would require a value of  $P_D = 0.05$  mgm. per cc.; *i.e.*, the diodrast clearance would not be depressed at values of  $P_D$  (1.0 to 3.0 mg. per cent) ordinarily used in this measurement. The last tubular tissue to saturate, having a perfusion rate approaching zero, would not saturate except at very high values of  $P_D$ ; but  $Tm_D$  can readily be determined at high values of  $P_D$ , where the load/ $Tm_D$  ratio = 3.0 or more, and hence the errors in  $Tm_D$  measurement can be reduced to negligible proportions.

#### VI. DISTRIBUTION OF GLOMERULAR ACTIVITY AND TUBULAR PERFUSION IN THE NORMAL KIDNEY

Figures 6 and 7 present data on the titration of normal subjects with glucose and diodrast. Important details relative to both groups of data are discussed in the legends.

In some subjects glomerular activity is so nearly uniform throughout the kidneys that no splay can be detected in the titration curve, *i.e.*, this curve closely follows the angle  $A'$  of Figure 5. Most subjects, however, show a slight splay, but this is so little that, in view of the practical difficulties in controlling  $P_o$  at precisely the proper level, it is difficult to get more than one or two samples of urine in the critical angle. For this reason no attempt has been made to present or analyze separately the titration curves of different individuals, all data being given in a mass diagram and averaged into a single titration curve (insert in Figure 6). Taking this curve as representing the average variations in glomerular activity, it may be said that in no appreciable number<sup>21</sup> of nephrons is glomerular activity below 0.60 or above 1.5 times the mean glomerular activity for the entire kidneys, and that the activity is distributed about the mean

<sup>21</sup> In view of the practical difficulties of slowly raising  $P_o$  over the critical range, and of the accurate collection of closely spaced urine samples, the above data do not represent the most rigorous application of the titration method, and in evaluating our present data we would not restrict the word "appreciable" to less than 5 per cent of the total tubular tissue.

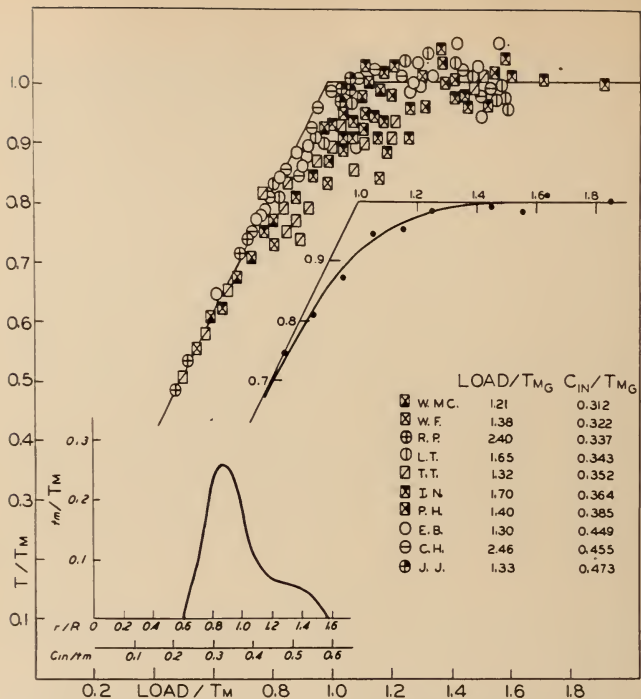


FIG. 6. Normal dispersion of glomerular activity. Mass plot of glucose titrations on ten normal subjects, some of whom were titrated on two or more occasions. The mass plot shows more scatter than is present in any one individual, but since one individual may be expected to vary slightly on different occasions, the mass plot may be taken as roughly representative of the normal variation.

For the calculation of the frequency distribution curve, the observations, of which there are 150, were averaged in blocks of  $\Delta \text{load}/T_m = 0.1$ . These averaged observations are shown in the inset, the smooth titration curve being drawn by visual approximation. The limits of relative glomerular activity are set at 0.60 and 1.50, since glucose excretion does not normally begin below a load/ $T_G$  ratio of 0.60, and, from the data presented in Tables I and II, we believe that  $T_{mG}$  is reached at a load/ $T_G$  ratio of 1.5.

The frequency distribution curve as drawn would indicate that in a small proportion of nephrons relative glomerular activity ( $r/R$ ) is greater than would be expected on chance distribution alone, with the consequence that the mode is shifted to slightly below the mean. It must be emphasized, however, that the use of data from different individuals, combined with the narrow limits of dispersion, caution against attaching significance to minor changes in the frequency distribution curve, which is extremely sensitive to changes in the angle of the titration curve. The above frequency distribution curve must be considered as practically identical with the symmetrical normal frequency distribution curve  $C$  shown in Figure 5. So interpreted, it may be said that glomerular activity in the normal kidney is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the observations fall within  $\pm 49$  per cent of the mean. (However, in some individuals, such as J. J., E. B., C. H., L. T., W. M., whose titration curves are sharply angular, the dispersion is so narrow that the glucose titration method is technically inadequate for a definitive examination. Subjects T. T. and I. N. pull the average titration curve out from the angle and are responsible for the skewing of the distribution curve to the right.)

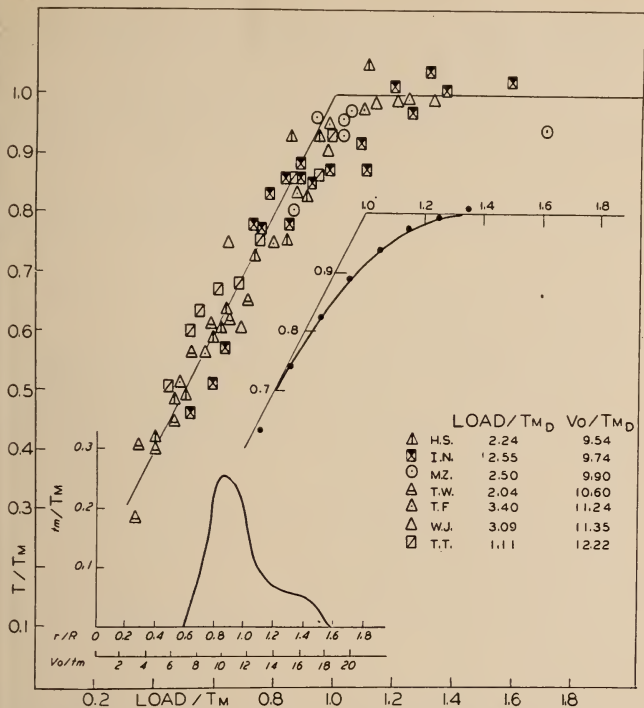


FIG. 7. Normal dispersion of tubular perfusion. Mass plot of diodrast titrations of seven normal subjects, some of whom were titrated twice. The mass plot contains 70 observations which were averaged by blocks of  $\Delta \text{load}/T_m = 0.1$ . The averaged data are shown in the inset, the smooth titration curve being drawn by visual approximation. The limits of relative tubular perfusion are conformably placed at 0.66 and 1.66. The lower figure cannot be set with accuracy, chiefly because of the error inherent in assuming a constant value for  $V_o$ , a difficulty discussed in the description of the diodrast titration method. The upper limit is taken as an extrapolation of the smooth titration curve, and is probably maximal. It must be recognized, however, that the uncertainty attached to the limits of the titration curve, and hence of the distribution curve, involves only a small percentage of the total tubular tissue.

As in the case of Figure 6, the frequency distribution curve is practically identical with the normal frequency distribution curve  $\bar{C}$  in Figure 5. The same qualifications must be applied to the massing of data obtained from different individuals as in the case of glucose titration. Accepting the curve as drawn, it may be said that *relative tubular perfusion in the normal kidney is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the observations fall within  $\pm 40$  per cent of the mean.* (Again it must be noted that in some individuals such as H. S. and T. S., whose titration curve is sharply angular, the dispersion is very narrow, while a few periods only on I. N. are responsible for much of the skew to the right.)

in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the nephrons fall within  $\pm 40$  per cent of the mean.

It is rather surprising that the filtration rate in various glomeruli, relative to the maximal reabsorptive capacity of the attached tubules, should be dispersed between such narrow limits, since both the size of the glomeruli (125 to  $246\mu$  in diameter in the dog) and of the (proximal) tubules (4.8 to 17 mm. in length) vary considerably in the mammalian kidney.

Our observations suggest that there is a close developmental correlation between the vascularity of the glomerular tuft and the functional development of the tubule connected with it, a relationship already noted by Shannon, Farber and Troast (31) in the dog's kidney.

In any case, these limits of dispersion are so narrow that we may confidently dispense with the presumed "reserve of inactive glomeruli" which has been used in the past to bolster pathologic and physiologic theory.

The diodrast titration curves of many normal subjects conform so closely to the sharp angle indicative of uniform tubular perfusion that it is difficult to detect the deviation by the present titration methods. Other subjects, however, show a definite splay, though whether or not this represents a consistent difference between subjects cannot be said from our present data. We have again averaged the observations on a number of subjects to obtain a median titration curve, and calculated the corresponding frequency distribution curve, as shown in Figure 7. The reader is referred to the legend for details.

Accepting the averaged curve as an adequate description, it may be said that in no appreciable number of nephrons is the tubular perfusion below 0.66 or above 1.66 times the mean tubular perfusion for the entire kidneys, and that the relative perfusion rate is distributed about the mean in a manner roughly conforming with the normal frequency distribution curve, the dispersion of which is such that 95 per cent of the tubular tissue is perfused at a rate within  $\pm 40$  per cent of the mean.

If we may speak of the normal "uniformity" of perfusion without contradiction of the frequency distribution curve as described above, we would note that this uniformity has an entirely different physiologic basis than the (statistically) comparable uniformity of glomerular activity throughout the kidneys. Until contrary evidence is available, we lean to the presumption that diodrast excretion is exclusively a function of the proximal segment, which is for the most part restricted to the renal cortex. In this view, the diodrast titration method reveals the perfusion rate chiefly of the cortical tubules. These, as indeed all other tubules, are in fact perfused not directly by blood but by interstitial fluid; each minute some 130 cc. of water are reabsorbed by the tubules to traverse the interstitial space and to return to the capillary bed;<sup>22</sup> and in view of the convolutions of the cortical tubules, as opposed to the more rectilinear arrangement of the capillaries, there is probably a considerable and perhaps very devious circu-

<sup>22</sup> It is estimated that some 80 per cent of this fluid is reabsorbed in the proximal tubule (41).

lation of this interstitial fluid which would operate to maintain uniformity of tubular perfusion even in areas where moderate to severe arteriolar lesions are present. Lastly, it should not be overlooked that tubular perfusion, as examined by the titration method, concerns individual tubule cells rather than entire nephrons, as in the case of glucose, and consequently physical diffusion of diodrast may contribute to the observed uniformity of perfusion. If such is the case, oxygen and other plasma solutes of higher diffusion velocity must be distributed even more effectively.

The above considerations relative to the physiological basis of the normal uniformity of glomerular activity and tubular perfusion, are obviously important in interpreting the course of renal disease.

#### VII. DISTRIBUTION OF GLOMERULAR ACTIVITY AND TUBULAR PERFUSION IN THE HYPERTENSIVE KIDNEY

Figures 8 to 13 present data on the titration with glucose and diodrast of seven hypertensive subjects. In examining the diseased kidney, it is necessary to consider each subject separately, since no two subjects can be expected to show comparable patterns in the renal circulation, and the reader is therefore referred to the accompanying legends for details of application and interpretations. We will note here only certain general features of the renal circulation in the diseased kidney.

Except for the two subjects who have only one kidney (fig. 8) no large block of ischemic parenchyma is observed. In three subjects (S. K., S. W. and Y. F.) the limits of dispersion in perfusion rate do not significantly exceed the normal; in three (E. F., A. M. and S. D.) the lower limit lies between 40 and 50 per cent of the mean normal value, while in only one (B. S.) it lies at about 30 per cent of the mean normal value.<sup>23</sup>

In sharp contrast to this tendency towards persistence of normal tubular perfusion, is a tendency towards abnormal glomerular activity. Out of seven subjects in whom glucose titration was successfully completed (five being shown here), five subjects (T. T., A. C., S. K., S. W. and B. S.) show as lower limits of relative glomerular activity 25 to 40 per cent of the mean normal value (to be compared with a lower limit of 60 per cent in normal subjects). This preponderance, even in a small series, of low glomerular activity implies the existence of arteriolar obstructive lesions.

Moreover, five out of seven subjects (T. T., A. C., S. K., S. W. and A. M.) show a definitely bimodal frequency distribution curve, notably illustrated by S. K. Such a bimodal curve implies that in large numbers of glomeruli the filtration rate has been reduced simultaneously, an effect to be anticipated if obstructive lesions were to occur in the larger arteries, in such positions that obstruction of one artery would reduce the filtration pressure in numerous de-

<sup>23</sup> It would be untimely to argue the physiologic significance of this or that degree of focal ischemia in the causation or course of the hypertensive process, especially since these patients were examined after bed rest and in an essentially basal condition, and we shall confine this discussion to an exposition of the methods as such.

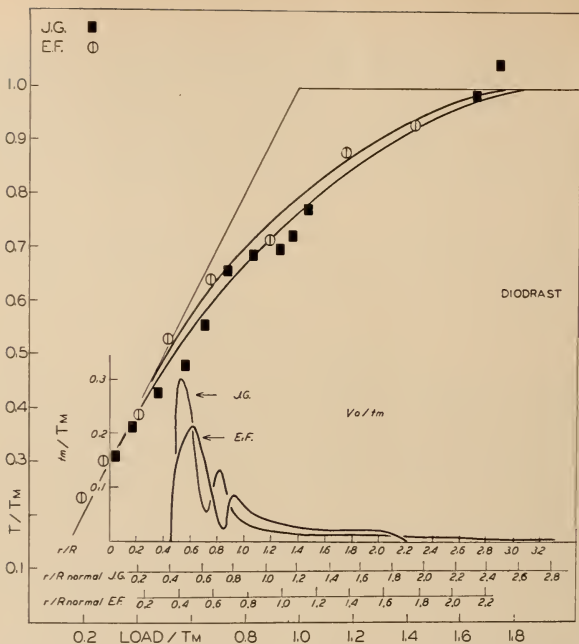


FIG. 8. E. F., 48 year old white female. Hypertension of many years duration, falling to moderate levels on bed rest. B.P. ranged from 230/130 to 160/86 mm. Hg. Heart enlarged; ECG showed left deviation; no evidence of congestive failure. Patient entered the hospital because of cerebral vascular accident. Retinae showed moderate vascular sclerosis, with normal discs and no hemorrhages or areas of degeneration. Urine was positive for protein, negative for blood. Concentrating capacity normal. Intravenous pyelograms showed no concentration of diodrast in the right renal pelvis; the left visualized normally. Right kidney removed on 1/26/42; diagnosis, atrophic pyelonephritic kidney. Diagnosis: essential hypertension; hypertensive and arteriosclerotic heart disease; cerebral vascular accident; atrophic pyelonephritis. On 2/12/40,  $C_D = 354$ ,  $C_{IN} = 83$ ,  $T_{MD} = 37.2$  (load/ $T_D = 2.0$ ), B.P. = 163/109. On 2/16/40 (titration)  $C_D = 416$ ,  $C_{IN} = 89$ , B.P. = 150/80,  $V_o/T_m = 9.44$  (79 per cent of normal). The titration curve is technically good, with no infusion hyperemia.

J. G., 45 year old white female. Hypertension of relatively short duration. B.P. ranged from 200/120 to 150/80 mm. Hg, falling promptly on bed rest. Heart not enlarged; ECG showed left deviation; no evidence of congestive failure. Retinae showed mild vascular sclerosis, with normal discs and no hemorrhage or areas of degeneration. Urine was negative for protein and blood. Concentrating capacity normal. Some years previous to these observations the right kidney had been removed for tuberculosis. There was no evidence of tuberculosis in the remaining kidney. Diagnosis: essential hypertension. On 1/9/42,  $C_D = 413$ ,  $T_{MD} = 40.7$  (load/ $T_D = 3.4$ ). On the day of titration (1/16/42),  $C_D = 463$ , which figure is used in the calculation. The titration curve is technically good, but  $T$  fell in periods 13, 14 and 15, concurrently with a marked fall in  $C_M$ .  $V_o/T_m = 10.1$  (85 per cent of normal).

In both of these subjects there has presumably been some compensatory hypertrophy of the tubules of the remaining kidney, since  $T_{MD}$  is considerably larger than one-half the mean normal value. Local disproportion in the hypertrophy of tubules and vascular channels may explain the increased dispersion of tubular perfusion, some tissue being extremely hyperemic, while a substantial fraction is quite ischemic. (The secondary modes in the distribution curves are attributable to the circumstance that, as drawn, the titration curves are nearly linear between load/ $T_D$  ratios of 0.9 and 1.4.)

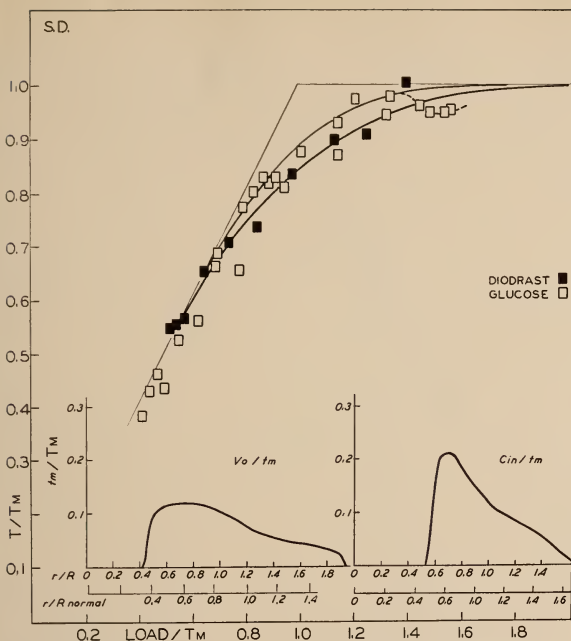


FIG. 9. S. D., 60 year old white female. Hypertension of many years duration. Blood pressure ranged from 224/130 to 186/118 mm. Hg. Heart enlarged; ECG showed left deviation of the electrical axis with inversion of the  $T$  waves in leads 1 and 2. No evidence of congestive heart failure. Retinae showed advanced vascular disease; discs normal; no hemorrhages or areas of degeneration. Urine negative for protein and blood; concentrating capacity normal. No history suggesting glomerulonephritis, pyelonephritis or uropathology. Intravenous pyelogram normal.

Died at age of 61 of cerebral hemorrhage. Diagnosis: essential hypertension with hypertensive and arteriosclerotic heart disease and cerebral arteriosclerosis. The patient had widespread arteriolar and arteriosclerosis. On 12/19/41,  $C_M = 51$ ,  $C_D = 216$ ,  $Tm_D = 14.8$  (load/ $T_D$  ratio = 7.7), B.P. = 212/120. On 12/23/41 with diodrast titration,  $C_M = 43.3$ ,  $C_D = 217$ ,  $Tm_D = 16.8$  (load/ $T_D$  ratio = 2.3), B.P. = 210/114. On 1/21/42 with diodrast titration repeated,  $C_M = 38.1$ ,  $C_D = 219$ , B.P. = 216/116. On 1/26/42 with glucose titration,  $C_M = 46.1$ ,  $C_D$  steady during titration at 185 to 222.  $Tm_G = 129$  (load/ $T_G$  = 1.1). B.P. = 216/114.  $V_o/Tm_D = 10.1$ , or 85 per cent of normal.  $C_{IN}/Tm_G = 0.358$ , or 91 per cent of normal.

This patient shows no decrease in mean tubular perfusion (100 per cent of normal) and only a slight decrease in glomerular activity (91 per cent of normal), while the frequency distribution curves relative to both functions deviate only slightly from the normal. There is a small quantity of tubular tissue which is perfused at a subnormal rate ( $r/R_{normal} = 0.4-0.6$ ) which is balanced by some hyperemic tissue having a perfusion rate as high as 80 per cent above normal. (The reader should compare this curve for  $v_o/tm$  with the normal curve in Fig. 7.) But this degree of deviation from normal is scarcely remarkable. Similarly, the distribution of glomerular filtrate is so nearly normal as to invite no comment, beyond the emphasis that in a 60 year old woman with hypertension of many years duration, and within one year of death, in whom the total filtration rate has been reduced to 40 per cent of normal,  $Tm_D$  to 37 per cent of normal, and  $Tm_G$  to 42 per cent of normal, the circulatory status of residual functional units is practically normal in pattern.

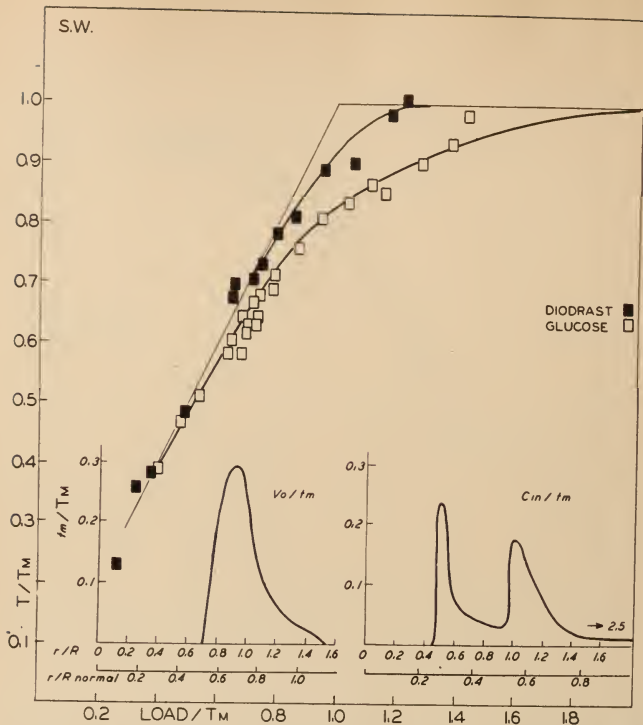


FIG. 10. S. W., 61 year old white male. Hypertension of many years duration. B.P. ranged from 220/128 to 190/110 mm. Hg. Heart enlarged; ECG showed left bundle branch block. No evidence of congestive heart failure. The retinae showed marked vascular sclerosis, with no hemorrhages or areas of degeneration and normal discs. Urine negative for protein and blood. Concentrating capacity normal. Clinical diagnosis: essential hypertension and hypertensive and arteriosclerotic heart disease. No previous history suggesting glomerulonephritis, pyelonephritis or uropathology. The clinical findings are indicative of widespread arteriolar and arteriosclerosis. On 11/21/40,  $C_D = 375$ ,  $C_{IN} = 74$ , with partial diodrast and glucose titration, B.P. = 230/135. On 11/29/40,  $C_D = 366$ ,  $C_{IN} = 71$ , followed by diodrast titration and partial glucose titration, B.P. = 200/110. On 12/6/40,  $T_{mD} = 36.5$  (load,  $T_D$  ratio = 3.1 to 4.22), B.P. = 194/112. On 12/11/40,  $C_D = 420$ , increasing to 594 during glucose titration, B.P. = 190/105.  $V_o/T_m = 8.63$ , or 74 per cent of normal. Glucose  $T_m$  (= 344) was determined on 12/11/40 at load/ $T_G = 1.38$  to 1.49. Partial titrations on 11/21/40, 11/29/40 and 12/11/40.  $C_{IN}/T_{mG} = 0.206$ , or 55 per cent of normal.

The total tubular perfusion of this subject is only 78 per cent of normal, but the distribution of perfusate is essentially normal.

The mean glomerular activity is only 55 per cent of normal and  $C_{IN}$ , which in 18 periods averages 71, is at the level of  $-2.7\sigma$  relative to the normal mean. Since  $T_{mG}$  is close to, though not above the mean normal value, it is inferred that this low glomerular activity reflects moderately severe impairment of the filtration bed. It will be noted that the subject is one of the few who falls so aberrantly in Figure 4 as to suggest some unusual feature in the glomerular or vascular bed. It is to be noted, however, that the mean tubular perfusion, which is distributed in an essentially normal manner, is reduced much less than is the mean glomerular activity.

The glucose titration curve is extrapolated in its upper portion; more uniform flexion would tend to lower the left-hand peak of the distribution curve and fill the intervening trough. As drawn, it indicates that the reduction in filtration rate is extreme in approximately 30 per cent of the glomeruli, but no tolerable change in the titration curve would entirely abolish bimodality, or the indication that some large proportion of glomeruli have an extremely low activity.

It is noteworthy that an essentially uniform perfusion of the tubules can be maintained in spite of vascular lesions so severe as to impair glomerular activity to this extent.

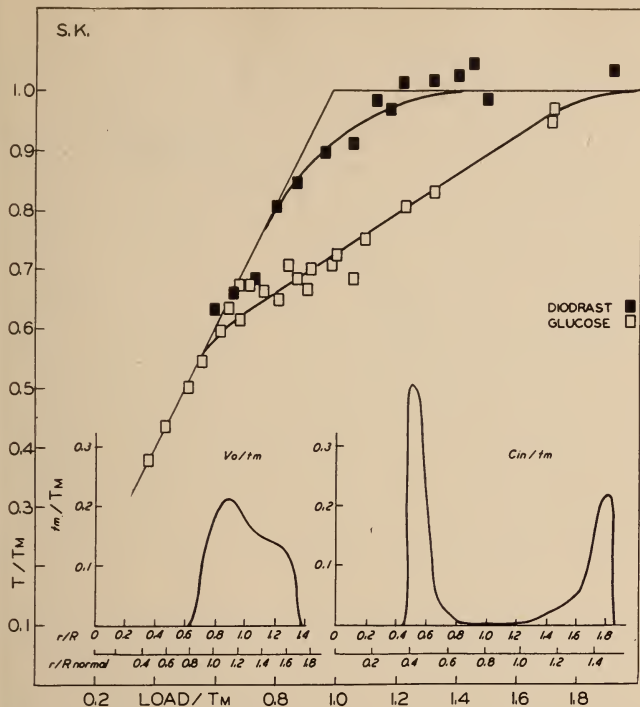


FIG. 11. S. K., 46 year old white male. Hypertension of relatively short duration. Blood pressure ranged from 210/134 to 140/100 mm. Hg. Heart enlarged; ECG showed left deviation of the electrical axis. No evidence of congestive heart failure. The retinae showed moderate vascular sclerosis, discs normal; no hemorrhages or areas of degeneration. The urine was positive for protein and negative for blood. Concentrating capacity normal. No previous history of glomerulonephritis, pyelonephritis, or uropathology. Retrograde pyelograms were normal. Diagnosis: essential hypertension. On 10/18/40 with glucose titration,  $C_M = 120$ ,  $T_{MG} = 410$  (load/ $T_G$  ratio = 1.73), B.P. = 138/92. On 10/23/40 with glucose titration repeated,  $C_M = 138$ , B.P. = 155/110. On 11/8/40 with glucose and diodrast titration,  $C_D = 718$ ,  $C_M = 130$ , B.P. = 142/99. On 11/15/40 with diodrast titration,  $C_M = 111$ ,  $T_{MD} = 43.3$  (load/ $T_D$  ratio = 2.6-4.7), B.P. = 152/110,  $V_o/T_{MD} = 14.5$ , or 125 per cent of normal.  $C_{IN}/T_{MG} = 0.300$ , or 81 per cent of normal.

This subject has a mean tubular perfusion rate 25 per cent above normal and a normal distribution of this perfusate, while the mean glomerular activity is only slightly below the normal (81 per cent); yet the distribution of glomerular activity is highly abnormal. A large number of glomeruli have an activity only 60 per cent of the mean, these being balanced by glomeruli having activities up to 80 per cent above the mean. Indeed, there are very few glomeruli with an activity equal to the mean.

In this instance, it must be supposed that localized arterial lesions have in effect divided the kidney into "affected" and "unaffected" glomeruli, while leaving tubular perfusion essentially undisturbed.

(It is possible that because of the low activity in some glomeruli, we had not reached definitive  $T_{MG}$  even at a load/ $T_G$  ratio of 1.73; but if  $T_{MG}$  is actually higher than our figure of 410, the effect on the titration and frequency distribution curves will be only to move the two modes away from the mean and to flatten the trough, i.e., to exaggerate the present picture.)

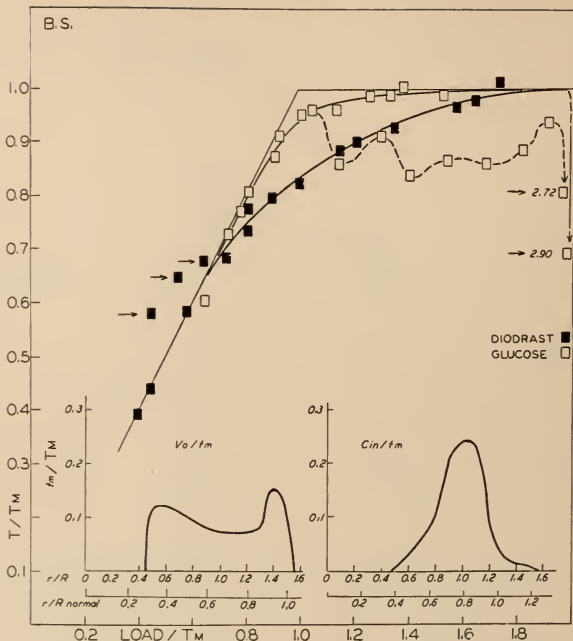


FIG. 12. B. S., 44 year old white female. Hypertension of relatively short duration. Blood pressure ranged from 210/100 to 140/68 mm. Hg. falling promptly on bed rest. Heart slightly enlarged and ECG normal. No evidence of congestive heart failure. The retinae showed no vascular changes and the discs were normal. Urine negative for protein and blood. Concentrating capacity normal. Clinical diagnosis: essential hypertension. No previous history suggesting glomerulonephritis, pyelonephritis or uropathology. There is no clinical evidence of widespread arteriolar disease. The fluctuating blood pressure, age of the patient and apparent short duration suggest the type of hypertension commonly seen in the climacteric. On 11/28/41,  $C_D = 356$ ,  $C_M = 101$ ,  $T_{MD} = 37.0$  (load/ $T_D = 1.9$ ), B.P. = 186/100. On 12/10/41,  $C_D = 357$ ,  $C_M = 81$ , B.P. = 162/88; during titration  $C_D$  increased to 426, from which figure  $V_o$  is calculated. Titration was repeated on 12/17/41, B.P. = 170/96, taking  $V_o$  as on 12/10/41; there was a transient hyperemia which lasted for 3 periods (arrows). (Also see below.)  $V_o \cdot T_{MD} = 8.0$  or 67 per cent of normal. Some uncertainty is attached to the titration curve as influenced by  $V_o$ , but no acceptable reinterpretation would abolish a wide dispersion.

First glucose titration was carried out on 1/14/42 (B.P. = 172/90), the infusion consisting of glucose in saline, 2.5 to 6.0 cc. per minute, and the patient having had only 200 cc. of water on the morning of the test. After period 5,  $T_G$  began to fall, as shown by the dotted line, ending at a much reduced value. We believe that this fall in  $T_G$  represents glomerular occlusion in consequence of the development of renal edema and increased intrarenal pressure. Titration repeated on 1/23/42, duplicating the procedures of 1/14/42 except that the infusion was made up in distilled water.  $T_G$  rose regularly to average 217 in 4 periods at load  $T_G$  ratios of 1.76 to 2.26, but after period 12 it began to fall, to end at 83 per cent of this value in period 15 at a load  $T_G$  ratio of 2.72 ( $P_G = 600$  mg. per cent). (Glo-

pendent glomeruli. Such lesions would tend to divide the kidney into two categories, "affected glomeruli" and "unaffected glomeruli," and thus break the frequency distribution curve into hypoactive and hyperactive glomeruli, using these expressions, of course, relative to the mean. It is conceivable that, consequent to such lesions, activity in the unaffected glomeruli might, by way of compensation, be increased, thus further separating the two categories in respect to activity. Relative to the last point,  $r/R_{\text{normal}}$  in the more active category in those subjects who show bimodal curves is *ca.* 0.6 (S. W.), 0.85 (T. T.), 1.1 (A. C.), 1.5 (S. K.) and 1.5 (A. M.); *i.e.*, in only two subjects is the activity of the more active category substantially above the normal mean. The question of compensatory increase in activity of "unaffected glomeruli" must be left to investigation.

The circumstance that even where arterial lesions have broken the pattern of glomerular activity into widely separated categories,<sup>24</sup> tubular perfusion may remain essentially unaffected is to be explained, we believe, on the basis that, first, the capillaries arising from the efferent arterioles undergo considerable anastomosis, so that blood from a normally "active" glomerulus may perfuse the tubule attached to a relatively "inactive" glomerulus; and secondly, as we have pointed out above, the circulation of interstitial fluid, coupled with simple diffusion, will tend to maintain uniformity of tubular perfusion in the face of

<sup>24</sup> Obviously, these two "widely separated" categories of glomeruli might be in the two separate kidneys. We have not attempted to apply the titration method to the two kidneys separately, and reiterate that at the moment we are discussing the method in principle and not in definitive application.

merular occlusion was apparently avoided on this occasion until the last 3 periods, and accordingly the maximal value, 217, is taken as  $Tm_G$ .

On both occasions the total filtration rate increased during the titration process, the rise amounting to an increase of 27 and 19 per cent above the initial value, indicating that an increase in glomerular activity occurred in other nephrons which more than compensated for the loss of the occluded units.  $C_D$  was followed throughout, and increased on both occasions *pari passu* with the filtration rate, maintaining a nearly constant filtration fraction (0.18-0.20).

Although both  $Tm_D$  (37.0) and  $Tm_G$  (217) are small, the ratio  $Tm_G/Tm_D$  (5.9) is in the lower range of normal, while the basal values of  $C_{IN}/Tm_G$  (0.330 to 0.400) range across the normal mean, and hence it appears that the total quantity of tubular tissue, both excretory and reabsorptive, is but little reduced. It is to be noted, however, that the relative tubular perfusion rate is the lowest of all subjects examined here ( $C_D/Tm_D = 9.65$ , or  $-2.08\sigma$  relative to normal standards). The filtration fraction as averaged from all observations is less than 20 per cent, a figure too low to permit this extreme ischemia to be explained on the basis of increased efferent tonus alone. The frequency distribution curve of tubular perfusion is exceptional in being flat and tending towards bimodality, suggesting gross impediment of large vascular areas. On the other hand, the frequency distribution curve of glomerular activity is also unique for hypertensive subjects, in that it is practically normal, indicating that there are no severe lesions in the arteriolar tree. This combination of circumstances suggests a clinically unrecognized disturbance in the kidney involving either renal edema (possibly of endocrine origin) or interstitial fibrosis, such that tubular perfusion is markedly impaired, although  $C_{IN}$  remains within the normal range, as judged either by surface area,  $Tm_D$  or  $Tm_G$ . Either suggestion is in line with the circumstance that this patient showed the greatest tendency to renal disturbance (edema and glomerular occlusion?) in consequence of infusion of glucose-saline solutions, of any of the subjects whom we have examined.

The data on this subject are interesting in that they demonstrate that a low rate of tubular perfusion will suffice to support glucose reabsorption, otherwise the severe ischemia of some tubules would lead to an increased dispersion of  $c_{in}/tm$ .

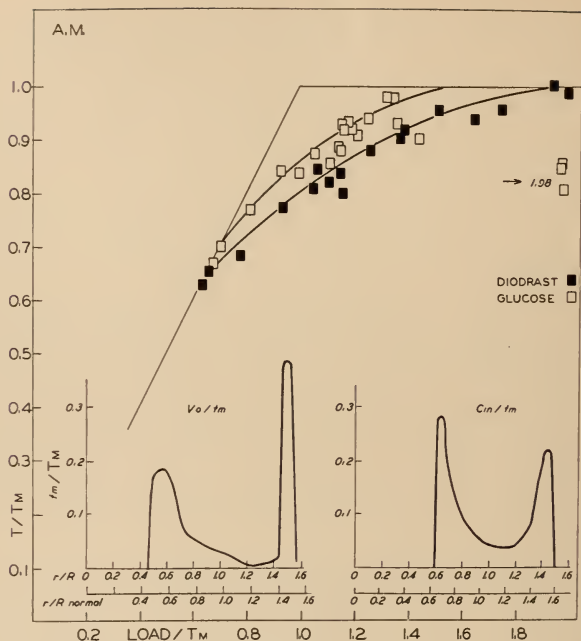


FIG. 13. A. M., 50 year old white female. Hypertension of relatively short duration. Blood pressure ranged from 165/115 to 138/80 mm. Hg, falling promptly on bed rest. The heart was not enlarged; the ECG showed low voltage and left deviation. No evidence of congestive heart failure. Retinae showed no vascular changes; discs normal. The urine was negative for protein and blood. Concentrating capacity normal. No previous history of glomerulonephritis, pyelonephritis or uropathology. Intravenous pyelogram normal. The patient showed the lethargy, skin changes, loss of hair and low voltage in the ECG suggestive of myxedema. The BMR was within the normal range. Diagnosis: essential hypertension. On 1/28/42 with diodrast titration,  $C_D = 378$ ,  $C_M = 65.4$ , B.P. = 162/88. On 2/2/42 with glucose titration,  $C_D$  increased during titration from 352 to 559,  $C_M = 77.7$ , B.P. = 152/90. On 2/9/42 with glucose titration,  $C_M = 89.4$ ,  $Tm_G = 211$  (load/ $T_G$  ratio = 1.55-1.92), B.P. = 142/74,  $C_D$  remaining between 524 and 666 during titration. On 2/16/42 with diodrast titration,  $C_D = 415$ ,  $C_M = 70.6$ ,  $Tm_D = 28.8$  (load/ $T_D$  ratio = 2.16-3.54), B.P. = 140/82. On 2/23/42 with diodrast titration,  $C_D = 399$ ,  $C_M = 62.6$ , B.P. = 132/80.  $V_m Tm_D = 11.6$  or 98 per cent of normal.  $C_{IX}$ ,  $Tm_G = 0.422$  or 107 per cent of normal.

Here both tubular perfusion and glomerular activity are abnormal in being bimodal, though the mean of both functions is somewhat above normal. On one occasion,  $T_G$  fell in the latter part of glucose titration, and at a load/ $T_G$  ratio of 1.98, to 80 per cent of  $Tm_G$ , indicating occlusion of glomeruli. This phenomenon was much more evident, however, in B. S. (fig. 12). It must be inferred that in this patient renal lesions are such as to impair the circulation to both glomeruli and tubules, though why tubular perfusion is impaired here to a so much greater extent than in our other subjects is unexplained.

local arteriolar disease. Our present data argue against the belief that local tubular ischemia is readily obtained.

It is worthy of note that where glomerular activity has a sharply abnormal pattern, while yet the mean is essentially normal, the abnormal pattern tends to consist of bimodal curve wherein those glomeruli of low activity are balanced by a large number of moderately active glomeruli, rather than by a diminishing series of glomeruli having progressively greater activity. Were the latter the case, relatively high values of glomerular activity would have to be reached in some nephrons and in consequence these nephrons would spill glucose at relatively low plasma glucose levels. The circumstance that hypertensive subjects do not typically show glycosuria suggests that the subjects we have examined are, in this respect, typical of the disease, rather than exceptions.

#### VIII. OCCLUSION OF GLOMERULI

One point requiring emphasis in closing, is the tendency of some subjects to show a marked decrease in  $T_g$  during the course of glucose titration or determination of  $Tm_g$ . This is particularly well illustrated by B. S. (fig. 12). This paradoxical fall in  $T_g$  has, in our experience, occurred only after some 90 to 150 minutes perfusion with saline-glucose solution mixtures containing mannitol but negligible quantities of diodrast at the rate of 4 to 6 cc. per minute. However, we have demonstrated that while maintaining a load/ $T_g$  ratio of 0.9 to 1.3,  $T_g$  may be substantially lowered by the more rapid (20 to 30 cc. per minute) infusion of 1000 cc. of saline.<sup>25</sup> We believe that it is the fluid rather than the glucose, mannitol or diodrast which is responsible. The explanation of this phenomenon is obscure, but we would suggest as a possible explanation that when fluid, and notably saline, is presented to the body too rapidly it tends to cause renal edema, and consequently to increase intrarenal pressure. This pressure could act to reduce the filtration rate in at least some glomeruli, particularly those in or near the *cortex corticus*, perhaps even to the point of complete occlusion. A fall to  $T_g$  of 20 to 30 per cent has been observed under these conditions (A. M., fig. 13, B. S., fig. 12), but it is not beyond possibility that nearly this fraction of glomeruli could be completely occluded, or the filtration rate so reduced in a complementary fraction as to effect this reduction in  $T_g$ . This explanation is tentative, and useful only until the phenomenon can be examined more thoroughly; but, if correct, it indicates that increased intrarenal pressure associated with intrarenal edema may play an important part in determining the frequency distribution of glomerular activity in disease.

Perhaps the most interesting part of this glomerular occlusion is the circumstance that it is generally accompanied by an increase in total filtration rate and in effective renal blood flow (see  $C_D$  data in figs. 10, 12, 13).<sup>26</sup> There is evidence that edema of peripheral tissues is frequently accompanied by hyperemia, and

<sup>25</sup> Partial glucose titration curves of normal subjects before, during and after saline administration were described at the Chicago meeting (1941) of the Federation of American Biological Societies.

<sup>26</sup> Space does not permit inclusion of the data, but the increase in effective renal blood flow is generally accompanied by a proportional increase in filtration rate, indicating afferent arteriolar dilatation. Shannon (30) has shown that saline infusion increases the filtration rate in the dog, and from the glomerular dynamics in this species it may be surmised that there is simultaneously renal hyperemia.

the above observations indicate that the kidney similarly responds to edema by hyperemia, effected by dilatation of still active glomeruli.

If the above interpretation is correct, it brings out the weakest point in the glucose titration method, *viz.*, that the administration of large quantities of saline (plus glucose ?) is apt to distort the normal pattern of glomerular activity. We believe that we have excluded from the experiments presented here those in which this complication is serious, but the difficulties presented by this hazard, especially in hypertensive subjects, are considerable. We hope that before the titration method is extensively applied a substitute for glucose, which can be administered in small quantities and in small amounts of saline, can be made available so that the hazard may be wholly circumvented.

#### SUMMARY

1. A brief résumé of the problems presented by possible intermittency of glomerular activity and tubular perfusion is presented.

2. Data are given on the maximal rate of glucose reabsorption ( $Tm_G$ ) in 24 men and 11 women without evidence of renal disease. Supplementary data are included on the filtration rate ( $C_{IN}$ ), the diodrast clearance ( $C_D$ ) and the maximal rate of tubular excretion of diodrast ( $Tm_D$ ) in these same subjects in order to permit a comparison of these data with  $Tm_D$ .

$Tm_G$  and  $Tm_D$  are not significantly modified by adrenalin, caffeine, or pyrogenic hyperemia, indicating the intrinsic stability both of the underlying tubular mechanisms of reabsorption and excretion, and of the glomerular and tubular blood supply. Since saturation of the glucose reabsorptive mechanism does not modify  $Tm_D$ , and *vice versa*, and since both tubular reabsorption (glucose) and tubular excretion (diodrast) are probably localized in the proximal tubule, it appears that independent chemical mechanisms may co-exist in the same tubule cell.

3. The statistical means in the present series of normal subjects in respect to  $C_{IN}$ ,  $C_D$  and  $Tm_D$  are in good agreement with the data presented in a previous paper. The previous and present series have been combined to afford new statistical references, the data on the sexes being treated separately since they differ significantly.

$Tm_G$  is positively correlated with  $C_{IN}$ , suggesting a developmental relationship between the rate of filtration in a particular nephron and the reabsorptive capacity of the attached tubule.  $Tm_G$  is poorly correlated with  $Tm_D$ , showing that the reabsorptive and excretory capacities of the tubule may be developed quite differently in the same individual, and presumably in the same nephron.

4. Data on  $Tm_G$  and other functional measurements are presented on subjects with essential hypertension. In these subjects  $Tm_G$  tends to remain within normal limits, being reduced only after a marked reduction in  $Tm_D$  has occurred; and the ratio  $C_{IN}/Tm_G$  adheres closely to the normal ratio, indicating that glucose reabsorption is not specifically impaired in hypertensive disease,  $Tm_G$  being reduced only after the glomerulus of a nephron is obliterated by vascular changes and the tubule thereby cut off passively from reabsorptive activity.

The reduction in  $Tm_D$  is the earliest characteristic impairment in renal function so far observed in hypertensive disease. If tubular excretion represents a final step in a series of metabolic reactions in the kidney, this impairment may have special significance.

5. It is assumed that the maximal rates of reabsorption of glucose ( $Tm_G$ ) and excretion of diodrast ( $Tm_D$ ) which characterize the over-all activity of the two kidneys, reflect similar quantitative limitations in each nephron. Under this assumption, the titration of the kidneys by the progressive elevation of the glucose or diodrast concentration in the plasma affords a means of measuring glomerular activity and tubular perfusion in component portions of the kidneys.

Glomerular activity is defined as the rate of glomerular filtration in cc. per minute per unit of glucose reabsorptive tissue in the attached nephron; while tubular perfusion is defined as the rate of flow in cc. per minute per unit of tubular excretory tissue of a fluid having the same concentration of diodrast as the post-glomerular plasma.

These titration methods have been developed in a quantitative manner and applied to the determination of the dispersion of glomerular activity and tubular perfusion in normal and hypertensive subjects.

6. In normal subjects no appreciable number of nephrons have a glomerular activity below 0.60 or above 1.5 times the mean glomerular activity for the entire kidneys; the glomerular activity being distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the nephrons fall within  $\pm 40$  per cent of the mean. That is to say, there is no large number of nephrons (*i.e.*, the fraction is no greater than 5 per cent) in which glomerular activity is less than 60 per cent of the mean; hence the notion of "glomerular reserve" posited on an assumption of glomerular intermittency carried over from cold-blooded vertebrates, is untenable.

In normal subjects no appreciable quantity of tubular tissue has a perfusion rate below 0.66 or above 1.66 times the mean tubular perfusion for the entire kidneys; the relative perfusion rate is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the tubular tissue is perfused at a rate within  $\pm 40$  per cent of the mean.

7. By way of example, rather than as a definitive study of the disease, the data obtained by the application of the titration methods to seven subjects with essential hypertension are given in detail. Several notable features emerge from this study:

The distribution of tubular perfusate and glomerular activity may be entirely normal despite long-standing hypertension.

There is an evident tendency for tubular perfusion to persist within the normal range and to maintain a normal pattern, in subjects in whom glomerular activity deviates from the normal pattern by separation into extremes of hypoactive and hyperactive glomeruli (both terms being used here relative to the subject's own mean of glomerular activity, and not the normal mean, which is

infrequently exceeded). This result is interpreted as indicating that arterial lesions may affect large numbers of glomeruli adversely, while anastomoses of the post-glomerular capillaries and the circulation of interstitial fluid operate to maintain uniformity of tubular perfusion. It seems apparent that focal tubular ischemia will prove to be the exception, rather than the rule, in the hypertensive kidney.

8. The administration of saline may reduce  $Tm_{\text{G}}$ —a phenomenon tentatively attributed to the production of renal edema and increased intrarenal pressure. There is usually a simultaneous increase in the total filtration rate and effective renal blood flow, indicating that renal edema (if this is the correct explanation) is accompanied by hyperemia, as is the frequent case in other tissues.

The analysts in this work have been Katherine S. Tilson, Betty J. Crawford, Frances E. Marx, Martha J. Barrett and Helen Claire Lawler. We are indebted to them, and to nurses Helen R. McGuire, Ann S. Rivoire and Agatha A. Evaskitis for their unfailing co-operation.

The clearance technique and analytical methods used in this study were identical with those described in a previous paper (19) except for the substitution of Albert's (3) iodine method, allowing 94 per cent recovery of diodrast in a 1:15  $\text{CdSO}_4$  filtrate, and Shannon's (31) glucose method. The inulin was ampouled material obtained from the U. S. Standard Products Company, Madison, Wisconsin, and the diodrast from the Winthrop Chemical Company, New York. Saline and glucose solutions (50 per cent) were prepared by Schering & Glatz, Inc., New York, to whom we are indebted for several lots of specially prepared glucose solution. The mannitol was supplied by courtesy by Sharp and Dohme, Philadelphia.

We are particularly indebted to Dr. H. M. C. Luykx for his valuable mathematical criticism and for his help in relating the titration to the frequency distribution curve.

#### Erratum

Two subordinate equations, used in the calculation of the ellipse in Figures 1 to 4 inclusive, contain typographical errors as given in our previous paper ((20) p. 638) and should read:

$$x = \frac{-ay}{2} \pm \sqrt{\left(\frac{a^2}{4} - b\right)y^2 - c}$$

$$c = -(1 - r^2)\chi^2\sigma^2$$

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## OBSERVATIONS ON CHANGES IN VOLUME OF SMALL VESSELS IN THE FINGERS AND TOES OF NORMAL YOUNG AND OLD PERSONS AND IN ARTERIAL HYPERTENSION<sup>1</sup>

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It would not be appropriate to celebrate Dr. Vineberg's lifetime of activity with an account of a mere analytical research. Because his own activities have been predominantly clinical we write out a description of an investigation now current which had its inception in the observation long established that many persons even in the third and fourth decades suffer from high blood pressures. Not many years back there was still doubt on the relative significance of the diastolic pressure as the significant one in an ailment now classified as "arterial hypertension".

This study began with the reflection that if the diastolic pressure is high in some way the occasion for this phenomenon must be found in the behavior of the small vessels. At this point Dr. George Burch came as a Commonwealth Fellow to the Hospital of the Rockefeller Institute and brought with him technical experience of Turner's plethysmograph. When all the conditions which make for uniformity are worked out, results are obtained as free as now seems possible from the influence of the environment. The temperature and humidity of the room are kept constant. The room is quiet, a minimal number of attendants coming in contact with the person being studied. The room itself is rendered free of all but an irreducible amount of apparatus suggestive of a laboratory. The room, in short, is made to look like an ordinary bedroom, and on this account saves persons from the impression of strangeness which in itself serves to act as a stimulus, to those who, especially in this condition, are susceptible to untoward psychological influences.

In this way records can be obtained which give quantitatively an exact account of changes in volume. A small cup, cut to measure, is put upon the tips of the fingers, the toes, and on the pinna of the ears. The records are made optically with Frank capsules reflecting light connected to the cup of the plethysmograph through rubber tubing. On the recording camera, movement of several capsules, reflecting, of course, movements in the fingers and toes and ear, can be inscribed simultaneously. The custom has been to study the tips of the right index finger, of the right second toe, and the pinna of the right ear.

At first it was essential to study the meaning itself of the records. They exhibited, of course, the fact that the pulse occasioned by the beating of the heart was inscribed and along with it the changes which reflected respiration. Such waves are already well known. In addition it was possible to decipher waves of

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a slower nature which could not be interpreted otherwise but as the result of the waxing and waning in size of the entire part. Three such waves called arbitrarily, alpha, beta and gamma have been identified. To attempt to trace out the meaning of the alpha waves alone has occupied our entire attention these several years past.

At first the inference seemed justified that the shape, frequency, and size of alpha waves were characteristic of persons depending on their psychological habitus. The conclusion was drawn that an individual yielded curves always of the same appearance. Later on, after more extended observation, it seemed that within limits, records which at first seemed invariant exhibited modifications which changed as a result of intellectual processes or of emotional occurrences not otherwise detectable on the surface, going on in the person who was experiencing them. That this interpretation is likely arose from knowing that during the period of observation the conditions of the external environment remained unchanged and also because in this particular phase of the study, the persons studied were trained psychologists and psychiatrists, persons in short capable of giving a good account of what had gone on within themselves during the period of observation.

Special papers will, of course, be consulted by those who wish detailed information of the results of these various studies. In this report it will be enough to point out certain general results. It is now known that changes in volume in a finger, a toe, or in an ear and in an opposite finger, toe and ear, need not be in the same direction at the same time. It was striking to learn, and this is the first yield connected with the object on account of which this investigation was undertaken, that a difference exists among normal younger people, normal older persons, and persons suffering from arterial hypertension. It was also found that in hypertensive individuals, sensitivity to stimuli seemed more acute than in the others. At first, before this fact was appreciated, and before for this reason an ordinary bedroom rather than a laboratory was made the scene of the study, hypertensive persons seemed to remain practically uninfluenced by artificial external stimuli. But when they were examined in a relaxed condition in a proper room, they turned out to be reactive in much the same way as other people, except that the speed of the reaction was greater and the duration after the cessation of the application of stimuli more protracted.

These studies are going on to attempt to discover the mechanisms which account for the phenomena which have been observed. The supposition now is that this is a neuro-muscular mechanism and that in all probability the sympathetic nerves to the vessels rather than the smooth muscle in their walls is the tissue chiefly reactive. There are a number of ways in which the participation of the sympathetic nerves can be ascertained both in the clinic and in experiments on animals. But to describe these would require a more extended narrative than is appropriate here.

It would, we thought, please Dr. Vineberg to know of these researches and so it seemed right to bring them to his notice.

It is with great pleasure that we tell him of our activities knowing well that what we do cannot be undertaken without the labors of those men of insight and of assiduity who have been our teachers. It is with the liveliest pleasure that we express our best wishes to Dr. Vineberg and wish for him continued enjoyment of the use of his faculties in sound health.

These studies were undertaken in association with Dr. George E. Burch, Dr. Charles Neumann, Dr. Colter Rule, Dr. William H. Lhamon, Dr. Edward A. Sellers. It is they who have been chiefly concerned, through procedural operations, with accumulating the data on which this narrative is based.

## QUANTITATIVE PREGNANCY TESTS IN THE DIAGNOSIS OF HYDATID MOLE AND CHORIONEPITHELIOMA

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The etiology of chorionepithelioma was not understood until Marchand (1) recognized its derivation from the chorion epithelium in 1895. Thus he segregated tumors, previously diagnosed as peculiar carcinomata or sarcomata, mainly of the uterus. Marchand likewise described the three histologic varieties encountered—typical, atypical and syncytiomatous. Frequent attempts to improve this classification have been made (especially by Ewing (2)), but have added little to the efforts of pathologists and clinicians to correlate morphology with malignancy. No other group of tumors shows as great a variation in this regard as chorionepithelioma. Chorionepithelioma of the uterus arises most frequently from an antecedent molar pregnancy, next from abortion, still less often from pregnancy at term, and least from tubal gestation.

A huge casuistic has accumulated, acquainting the profession with the protean clinical manifestations and varying course of these growths. Metastases have been noted in practically every organ of the body (3). Variations in the latent period, dating from the origin during pregnancy up to latency of 8 to 15 years are on record (4). The degree of malignancy varies from the very rare spontaneous regression, particularly of metastases after the primary growth has been removed, to rapid extension and death within weeks. Secondary symptoms such as gynecomastia in the male, polylutein cystic enlargement of the ovaries in the female, accentuated pregnancy changes in the adenohipophysis (5), take place. The common site of origin of both hydatid mole and chorionepithelioma are in the uterus, most often endometrial, not infrequently interstitial in the musculature. A number of cases of chorionepithelioma in tubal pregnancies have been found (6). Parthenogenetic origin in teratomatous growths in both sexes are not infrequent, ovarian in the female, testicular in the male, mediastinal and retroperitoneal in both sexes (7). Such derivation is ascribed to origin from the totipotent cells of the host's own anlage.

The clinician frequently is confronted by difficulty in diagnosis, as well as by the dilemma of deciding upon the best, and particularly in young patients, the least destructive therapy. Vineberg (8) made a valuable contribution in 1919 by advising both digital and visual exploration of the uterine cavity in doubtful cases in which curettage had proved either negative or inconclusive (sessile or interstitial location). His clinical acumen during these formative years in which chorionepithelioma was regarded as a rare condition, enabled him to save patients by early diagnosis and radical operation. At that time the sole method of arriving at a conclusive decision depended upon the recognition of the growth by histologic examination of the curettings. Inaccessible intramural location gave negative curettings. Moreover, histologically atypical growths were not correctly diagnosed in some instances even by experienced pathologists, or non-

pathologic overgrowth of the epithelial covering of the villi was erroneously interpreted as malignant.

This situation has been greatly improved since the introduction of pregnancy tests, particularly the *quantitative* pregnancy tests. The Aschheim-Zondek test or its modifications, depended upon the increase of gonadotropic factors circulating in the blood and excreted in the urine. This increase occurs within a few days after fertilization but does not remain at a constant level throughout pregnancy. This was recognized by Zondek and more carefully studied by Evans (9). The latter showed that between the thirtieth and fiftieth day following the expected but missed period, a tremendous peak of gonadotropic secretion and excretion occurred, and that before and after this period of pregnancy, a more constant but lower level obtained. Therefore experience and critique are essential in evaluating the quantitative pregnancy test. Unless the peak period is taken into consideration, mistakes are bound to occur.

When the Aschheim-Zondek test was first introduced, I personally was misled twice in patients between the first and second months, who showed an increase of several hundred times the gonadotropic factors in the urine, and upon whom I mistakenly made the diagnosis of chorionepithelioma because of the outcome of the test and the clinical symptom of bleeding. Upon emptying the uterus in both cases, early normal pregnancy was encountered.

No definite figures are available on the lowest normal titers to be expected with the four day Aschheim-Zondek test or its modifications which we have used in our laboratory. These include the 48 hour Friedman test on rabbits and the 24 hour test published from our laboratory, using immature rats (10). The original Aschheim-Zondek test for the diagnosis of pregnancy, employs four varying amounts of urine (1.2 cc. to 2.4 cc.). The Friedman test uses 20 cc. intravenously. Our test employs 10 cc. subcutaneously. The levels in these tests decided upon, i.e., the total amount of urine routinely injected, was determined by choosing a level below the amount excreted by menstruating or menopausal women, and yet sufficient to give a positive reaction in the early period of pregnancy before the peak is reached. This is somewhat aided by the fact that in the non-pregnant the follicle stimulating factor predominates quantitatively over the luteinizing factor, the latter being greatly increased after conception. It must furthermore be recognized that pregnancy tests do not differentiate between hydatid mole and chorionepithelioma (11). This is unfortunate because hydatid mole *per se* is not malignant; the relationship between hydatid mole and chorionepithelioma in many ways resembling the variation between adenoma and carcinoma. The pregnancy test does not differ in the male and in the female. It should likewise be remembered that certain non-chorionepitheliomatous testicular tumors such as seminoma and dysgerminoma, as well as adrenocortical carcinoma, may produce follicle stimulation in the test animal but fail to luteinize their ovaries unless widespread metastases develop.

It should be mentioned that although the estrogens in the urine and in the blood increase progressively throughout normal pregnancy (12), as far as our experience allows us to judge, this does not appear to hold true in hydatid mole

and chorionepithelioma. Taking into consideration the fact that we have repeatedly noted a prompt disappearance of the estrogens circulating in the blood after fetal death (13), the absence of estrogens or low titer of blood estrogens in hydatid and chorionepithelioma may have more than a theoretical importance in explaining the overgrowth of fetal placental elements. We have had no opportunity of studying the very rare cases where molar pregnancy and a live fetus co-exist.

After the complete elimination of a non-malignant hydatid mole (either spontaneously or by curettages or hysterectomy) or the radical removal of a chorionepitheliomatous tumor, the pregnancy test becomes negative, usually within a week. Until there is recurrence, or metastatic deposits are already present in chorionepithelioma; removal of the primary tumors likewise is followed by negative pregnancy tests. It is not uncommon that a period of negative pregnancy tests are noted until metastases occur, and therefore it is essential that in suspected cases a repetition of the test be performed at monthly intervals and later at progressively increasing intervals for long periods of time, in order that metastasis can be diagnosed early, because such secondary deposits may be radiosensitive and patients have been saved by radiotherapy or their life span markedly prolonged.

Our experience is based on 27 cases in which pregnancy tests have been performed, 16 of chorionepithelioma, 11 of hydatid mole. Two cases of chorionepithelioma of the uterus which were observed before pregnancy tests had been discovered, are not included. In both of these, blood estrogen tests showed no increase. In the early days not all of the pregnancy tests were quantitative. The sex distribution consisted of 16 females and 11 males. Hydatid mole occurred only in females; the presence of hydatid elements alone, in testicular tumors or other teratomata being extremely uncommon.

Analysis of our data shows the following: There were 11 males with chorionepithelioma, 8 of which showed metastases. In 3, metastases were suspected but not demonstrated. Location of the primary tumor was testicular in 5; pulmonary in 2; retroperitoneal in 1; mediastinal in 1; bladder in 2. Without metastases when first observed, there were 1 testicular and 1 mediastinal (teratoma) growths.

Of the 16 females, 5 showed chorionepithelioma (4 uterine, 1 ectopic). Only 2 of these patients had metastases. Of the 11 hydatid carriers, none showed metastases.

*Pregnancy tests:* The pregnancy tests carried out on 27 patients were 5 typical Aschheim-Zondek non-quantitative; 15 Friedman tests, all quantitative; 7 Frank-Berman tests, all quantitative. Of the Friedman tests, the lowest titer was .025 cc. obtained in a male with testicular tumor and metastases. The lowest Frank-Berman test was .0025 in a female carrying an hydatid mole. The average low titers obtained with the Friedman test lay between .25 cc. and .03 cc. The average for the Frank-Berman test was .05 cc. There was evidence that with appearance of metastases, the gonadotropic factors increased abruptly.

From the above it will become apparent that no hard and fast figures of dilu-

TABLE 1

LAB. NO.	SEX	AGE	CHORIO	HYDATID	SITE	METASTASIS		URINE PREGNANCY TESTS			PREGNANCY TEST		ES. TEST	
						Yes	No	A-Z	Friedman	F-B	Blood	Blood	Blood	Urine
1848	F	32		x	Uterus		x	pos. 1.2				pos. 40 cc.	400 MU/L	42 days later A-Z neg. Tests repeated during 3 yrs. neg. Bl. serum pos. to .005 cc.; test neg. 2 mos. later. Bl. serum pos. to .0075 cc. Hysterectomy. Bl. serum pos. to .05 cc. Uterus and tubes normal. Test remained positive for 13 days post-op. Test positive for 2 mos. Well 7 yrs. later. Had expelled mole spontaneously 3 wks. ante. Hysterectomy. Test neg. 6 days post-op.  Hysterectomy 3 months before. Androgen excretion low (5.68 mg/L) In menopause; hydatid 3 yrs. ante. Hysterectomy. Test neg. 10 days post-op. Hysterectomy. Test neg. 4 wks. later.  Gyneconastia. 1 gm. tumor tissue gave A-Z pos.  Test positive 6 days post-orchidectomy Pericardial fluid pos. .05 cc.  Later test pos. to .0075 cc. (135,000 Rat U/L)
2392	F	41		x	Uterus		x		pos. 6 cc.		.005 cc.	neg. 50 cc.		
2729	F	28		x	Uterus		x	pos. 0.21	pos. 1 cc.		.0075 cc.	neg. 40 cc.		
3014	F	26		x	Uterus		x				.05 cc.	neg. 40 cc.		
3018	F	22		x	Lung		x		pos. .25		.005 cc.	neg. 40 cc.	neg. 2 cc.	
3186	F	31	x		Uterus		x		pos. .03			neg. 40 cc.	pos. 2 cc.	
3294	F	48		x	Uterus		x		pos. .1		.005 cc.	neg. 40 cc.		
3315	F	48		x	Uterus		x		neg. 20			neg. 13 cc.		
3390	F	30		x	Uterus		x		pos. 1.0					
4341	F	29		x	Uterus		x		pos. 20			neg. 40 cc.		
4502	F	32	x	x	Uterus		x		neg. 20					
5002	F	27	x		Uterus		x			pos. .05				50 MU/L 25 MU/L 65 MU/L  neg. 2 cc. 1300 MU/L
P103	F	57	x		Uterus		x			pos. 10.0				
P279	F	30	x		Uterus		x			pos. 1				
P535	F	43		x	Uterus		x			pos. .0025				
2116	M		x		Testis	?		pos. 1.2						
2188	M	29	x		Lung		x	pos. 1.5						
2367	M	22	x		Lung		x	pos. 1.5						
2890	M	51	x		Testis		x		pos. .1					
3035	M	21	x		Testis	?			pos. 1.					
3246	M	23	x		Retro-peri-ton.		x		pos. 1.		pos. .0175			
4377	M	70	x		Bladder		x		pos. 1.				neg. 2 cc.	1300 MU/L
4458	M		x		Testis		x		pos. .25					
4514	M	13	x		Testis		x		pos. .05					
P59	M	22	x		Mediastinal	?				pos. .01				
P115	M	63	x		Bladder		x			pos. 1.				

tion can be stated at which a definite diagnosis of either chorionepithelioma or hydatid mole is justified. In the first place the peak occurring between the thirtieth and fiftieth day, as pointed out by Evans, must always be taken into consideration and can lead to serious error if not considered, as previously pointed out. The titer in hydatid mole appears to be lower than in chorionepithelioma of the uterus unless metastases have developed. This probably is accounted for by the fact that in hydatid, the chorionic tissue is larger in amount and contains more chorion epithelium than does the average uterine chorionepithelioma. On the other hand, in the male where metastases appear to develop earlier, low titers are the rule. From the fact that strong positive pregnancy reactions were noted in the case of seminoma of the testicle as well as in an adenocarcinoma of the adrenal after widespread metastases had developed, it appears that the pregnancy test is not strictly specific for chorionic tissue but may, in rare instances, be produced by other rapidly growing cells of embryonic type.

*Blood serum:* Pregnancy tests on the blood serum in doubtful cases are of great value. By the typical Aschheim-Zondek test, as little as .005 cc. gave a positive reaction in a patient with hydatid mole. Another showed .0075 cc. positive, although Evan's peak had been passed (fourth month of pregnancy). The urine titers in these cases were far above this level.

Examination of fluid obtained by aspirating the hydatid vesicles showed a positive reaction with .15 cc. by the typical Aschheim-Zondek test in one patient. In a patient with retroperitoneal chorionepithelioma, pericardial fluid obtained post-mortem, gave a positive test with .05 cc. (Aschheim-Zondek).

I have had no personal experience with pregnancy tests performed on cerebrospinal fluid. Several authors declare that a positive test is only obtained in hydatid mole and chorionepithelioma (14).

*Duration of the positive pregnancy test after expulsion of moles or postoperatively (either curettage, hysterectomy or orchidectomy):* Two patients expelled the moles spontaneously without subsequent curettage. In the one, the first pregnancy test obtained was found negative after three weeks, in the other, after two months. The latter has been followed for seven years and has shown no recurrence. The third patient with hydatid mole, who had a hysterectomy performed, showed a negative reaction three months later. In two cases of chorionepithelioma of the uterus, the reaction became negative, respectively, six and ten days after hysterectomy.

In both hydatid mole and chorionepithelioma, the fact that the pregnancy reaction becomes negative shows that the chorionic epithelium has been eliminated completely. Return of positive reaction signifies recurrence or metastases. Patients subjected to x-ray therapy show a diminution in the acuity of the pregnancy reaction and at times complete disappearance of the same. This can serve as a rough guide to the clinician as to the effectiveness but not of the permanence of radiotherapy. All patients should have repetition of pregnancy tests at monthly intervals for the first six months and thereafter at progressively greater intervals in order that the occurrence of metastases can be determined at the earliest moment and proper therapy instituted without delay.

Certain other facts not directly connected with the pregnancy test have been noted during this analysis of the data. From extraction experiments performed on metastatic deposits from the lung and liver tissue obtained at autopsy, it becomes evident that no real storage of hormones occurs in the metastases but that they are at once liberated into the blood stream. Furthermore, the estrogen contents of hydatid and chorionepitheliomatous tissues is far below that found in normal placental tissue, although the chorion epithelium is more abundant and more active than in normal placenta. This together with the almost universal low blood and urine titer for estrogens, likewise distinguishes hydatid mole and chorionepithelioma from normal gestation. How great a rôle the absence of a fetus plays cannot even be guessed at from the data at my disposal.

#### CONCLUSIONS

1. A positive pregnancy test signifies the presence of a pregnancy, including ectopic (tubal, ovarian, molar), or of chorionepithelioma (arising from pregnancy or teratoma). In very rare instances other tumors, after widespread metastases have developed, can give a typical pregnancy test.
2. The increase in gonadotropic factors, upon which pregnancy tests are based, reaches a tremendous peak between the thirtieth and fiftieth days in normal pregnancy.
3. In hydatid mole and chorionepithelioma, irrespective of origin, the gonadotropic factors are elevated above the level reached in normal pregnancy, *except the level attained during the peak period* (see 2).
4. Therefore the *quantitative* pregnancy test is of value only if the peak is kept in mind. This of course does not apply to a positive test in the male in whom no peak occurs.
5. A low estrogen blood or urinary titer, after the seventeenth week in the female, gives confirmatory evidence of the presence of a pathologic gestational condition (either death of fetus or presence of chorionepithelioma or hydatid).

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## NEURO-MUSCULAR DYSTROPHY DURING PREGNANCY AND LABOUR

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The subject of muscular cramps during pregnancy and labour has been under investigation in my private practice for the past three years, and, as a consequence, a great many facts have been accumulated upon this poorly understood subject. There has never been advanced any adequate theory to explain why the pregnant woman is so subject to muscular cramps, nor why these are carried over, in various manifestations, into the first and second stages of labour and into the puerperal state. It is not to be supposed that the theory to be expounded is adequate, because behind these manifestations of neuro-muscular dystrophies is a complex causation which, with our present incomplete knowledge defies complete analysis. However, the beginning of the elucidation of any subject should consist of an accumulation of observations bearing upon that topic, and when this has reached adequate proportions a theory will be evolved which best meets all the questions which revolve about the subject. This theory will then hold sway until further knowledge offers a more adequate hypothesis. So it is with the subject of neuro-muscular dystrophies. I will first outline the accumulated observations of the past years of experience and investigations, and then proceed to find an hypothesis that best explains these clinical phenomena.

Neuro-muscular dystrophy is a relative disease, that is, it has its almost imperceptible initial symptoms, and these may be met in gradation up to the most pronounced, distressing and dangerous proportions. Beyond these almost imperceptible symptoms must be a causation which, as yet, has not reached the degree of eliciting symptoms. That is true of every disease, that the cause must be in operation for some time and in a gradual progression before symptoms are developed. In other words, disarranged function precedes disease manifestations. The commonest manifestations of these dystrophies are found in cramps of the calf of the leg or in the plantar area of the foot. These usually arise upon first movement after a prolonged sleep. Usually the first muscular movement in the morning awakens these symptoms. Frequently they are so intense as to cause the patient to shriek with pain and the husband endeavours to assuage by massage and support. The acute stage of pain, in most instances, usually passes off in a very short time. In most cases, however, a soreness as if of a residual partial spasm remained for some time. Many times this residual pain may persist for a day or more, and is exaggerated upon using the involved muscles. The above type of the disease is commonly recognized by the physician and his explanation of muscular cramp usually satisfies the patient so that she bears the subsequent manifestations with more or less equanimity. However, the

recognition of the disease is not always so easy. It has been found that almost any muscle of the body, whether voluntary or involuntary, may become spastic, and depending upon its site and depth, may offer to the uninitiated almost insuperable difficulties in a differential diagnosis. Next to the muscles of the calf and foot, the thigh muscles are the most frequently affected. There is usually little difficulty encountered here in the diagnosis. But when the dystrophy attacks the abdominal region the diagnosis becomes one based upon experience and careful observation. The previous presence of cramps of the lower limbs in abdominal involvement may facilitate the tentative diagnosis by drawing the surgeon's attention to the type of disease, but the involved regions of the body may shift and the association of lower limb cramps may not be present. It is a singular observation that when one muscle or set of muscles becomes affected the symptoms tend to confine their repetitions more or less to these same structures, and just as stated above, the spasm may be short and sharp with complete relief, or soreness may persist for hours, even days, no matter what the structure involved. The uterus is frequently the organ affected. The cramp is like that of menstruation, often so severe as to cause the patient great distress. The uterus usually becomes prominent during the pain. The spasm affects only a part of the uterine wall, and, depending upon the site of this spasm and the subsequent tenderness will be whether the surgeon can elicit tactile corroboration of his suspicions. Of course, if the posterior wall of the uterus is the area affected, tactile corroboration is impossible. But on several occasions a local tumor of the uterine wall was found at the site of maximum pain and great tenderness was elicited on palpation.

Spasm of the round ligament is not uncommon. The pain is localized lateral to the uterus and is referred down the inguinal canal. I have had the opportunity of observing several of these cases.

Spasms of a part of one of the abdominal muscles may cause intense distress and inhibit all movement until the spasm has passed off. One of these cases had a definite mass over the left abdominal wall, tender and hard. The muscles were in a continuous state of spasm. The correct diagnosis of this was made by anesthesia and appropriate treatment.

The most difficult cases are those in which the deep muscles of the body are involved. These may simulate renal and hepatic colic so closely as to defy diagnosis for quite a time. A summary of a few of these cases will help perhaps in one's approach.

A patient whom I had known socially and medically for years was in her third pregnancy. She had had some muscular spasm of the legs which she tolerated well because she knew their significance. At 2 a.m. I was called for an intense pain in the region of the right kidney. I gave her at once a hypodermic of morphine, grain  $\frac{1}{4}$ , and waited. After twenty minutes there was no relief. I repeated the dose, again no relief. Heat had been applied upon my advice before my arrival. This patient was a woman who had disciplined herself and had wonderful self-control. So that I knew that her symptoms were genuine. I then catheterized her and took the urine at once to my office. I

centrifuged it and examined it carefully. There was a total absence of blood or pus. When I went back to her home she was still in severe pain, and this continued for almost 24 hours. She is a very intelligent woman and the daughter of a well-known doctor. She said to me, "I don't feel as though there were actually any disease, but it impresses me more like a cramp." Ten days later she had a similar but not so severe a repetition. Again morphine had no effect. A week later I did a Caesarian section for the third time. At the operation I examined the right renal region very carefully and found nothing abnormal. One half hour after the operation she had an intense attack. She was writhing in pain and morphine in large doses had no appreciable effect. This agony slowly abated but did not completely disappear for 48 hours. Every known form of examination was made during this time without revealing any departure from the normal findings. Her recovery was uninterrupted from then on, and there was no recurrence.

Another case involved the region of the gall-bladder. What muscles were involved I could never determine. I was called in a hurry to the case in the eighth month of her pregnancy. I had confined her previously four times. During the previous pregnancy she had suffered a great deal with leg cramps and abdominal pains. This time she had all the signs of a severe cholelithiasis. The pain was intense and was referred to the front and back right subcostal region. There was no shoulder pain. Morphine was administered in large doses without appreciable improvement. The pain subsided slowly and the patient was normal again after 24 hours. A few days later she had a similar attack. Visualization of the gall-bladder proved negative and microscopic examination of the urine also was negative. This patient had repeated similar attacks during the rest of her pregnancy and the abnormal state subsided upon delivery.

These are but two of a goodly number of categorical cases. One, a doctor's wife, had her gall-bladder removed during pregnancy for suspected stone, though x-ray examinations proved negative. Nothing was found at operation but her attacks continued off and on until the end of her pregnancy.

The frequency of abdominal neuro-muscular dystrophies is only now being appreciated. Hardly a week passes by without meeting some modification of the details given above, and they nearly all yield now to treatment. Moreover the comfort which the patient experiences when told that it is merely another form of her leg cramps is just another form of mental reassurance.

#### PRIMARY INERTIA UTERI

The major manifestation of neuro-muscular dystrophy is found in so-called primary inertia of the uterus. This is a very difficult subject, still much under debate, not only as to its causation, but also as to its *modus operandi*. Primarily, it may be stated, like all forms of disease, it is a relative state of pathology. Minor degrees of the disease, which border on the normal, are seen beside major types that pass definitely into gross departures from normal physiology and entail a corresponding degree of danger and probable morbidity to both mother and child. The "larval" degrees of inertia frequently pass unnoticed by the ob-

stetrician, whereas the major types are probably, of all obstetrical states, the ones which cause the greatest anxiety to the obstetrician during the prolonged hours of labour in such cases.

What is primary *inertia uteri*? Well, it is best to define it as a defect in the normal mechanism of the autonomic nervous system and in the physiology of the muscular structures that it supplies. To make it clearer, there are two types of inertia, primary and secondary.

Secondary inertia in a broad sense is fatigue after normal effort. A woman goes into labour, she has what would seem to be normal uterine contractions with a resultant effect upon the cervix. After a period the pains pass off and the effect ceases. The seemingly normal function which had taken place may be long or short. Labour from then on becomes comparatively ineffectual. The uterine pains may cease completely to be resumed after a rest, or the uterus may pass into a state of constant subjective discomfort and spasm. When "pains" cease completely the patient frequently resumes a normal period of uterine action during which she may complete her labour, or she may have repeated spells of secondary inertia. The cause of this fatigue may lie in the abnormal state of the neuro-musculature of the uterus, or in undue resistance to the normal uterine effort. An article entitled "The Inertia Syndrome" appeared in the *Journal of Obstetrics and Gynaecology of the British Empire*, 41: 256, 1941. In this article I outlined the main course and symptoms of primary inertia uteri. I shall quote extensively from this article, but the past two years of study have added much in the observation of facts and treatment that give the subject an added interest.

Primary inertia is detectable as a clinical entity only after labour has been in operation for some hours. The initiation of labour begins with spontaneous rupture of the membranes in about 40 per cent of cases, as compared with 20 per cent in normal cases. This, I believe, is due to the sudden spasm of the uterine muscle, causing a sudden increase in intrauterine pressure. This high percentage of initial ruptures adds a very grave factor to the labour, as will be pointed out later. Labour pains may be delayed for hours, even days, after the membranes have ruptured. *Per contra*, in normal cases of labour, pains generally follow quickly upon evacuation of the waters. The effectiveness of evacuation of the forewaters is seen in the adoption of this measure to bring on labour. In cases of inertia, where the bag of waters is maintained, pains set in and are at first indistinguishable from those of normal labour, except that in cases of inertia there is very seldom any "show." "Show" is an indication of the detachment of the membranes from the lower pole of the uterus by the expansion of the lower uterine segment under the effect of the upper uterine action. The absence of "show" in these cases of inertia is an index of the small effect which uterine action is having upon the lower segment. The membranes which bridge the lower uterine segment are unattached of course, not only over the os, but also for a distance of from one to two inches beyond the margin of the internal os. Time and again I have circled the free area within the os, and having defined its limits I have broken through the line of attachment and detached the membranes

from the uterine wall. This line of attachment is at times quite firm. When the membranes are intact and normal labour proceeds, the lower line of membranous attachment becomes extended by the expanding lower segment which is like a progressively stretching rubber band, and the membranes of the unattached part become increasingly taut, as a hammock whose attachments are being gradually moved wider apart. At last comes a time when the lower margin of membranous attachment can no longer follow the receding lower segment of the uterus, then one or both of two things must occur. Either the membranes pull away from the uterine wall, or the membranes must rupture to relieve the pressure, or both the above may occur simultaneously or separately. The detachment of the membranes causes a breach of continuity and slight bleeding occurs. The fact that there is commonly an absence of any "show" until some hours of "pains" have been suffered—hours which in many cases may run into days—is *prima facie* evidence of the slight effect of the action of the upper uterine segment upon the lower.

The "pains" of primary inertia usually differ from those of normal labour. This difference is seldom appreciable at first, but sooner or later, after the uterus has gone into action, one realizes that the patient suffers more than in normal labour because she is seldom completely free from pain. A residuum of distress, like that soreness which persists after a muscular cramp in the leg during pregnancy, remains between pains and prevents the patient from enjoying that pause that restores. This factor is variable in different cases. In some the interval is comparatively free; in others, the severity of the pains persists practically unchanged throughout what would normally be the interval when the hand is placed upon the uterus and the practiced fingers realize an unnatural hardness of the uterus that persists indefinitely. Frequently the uterus contracts more forcefully in certain areas giving rise to conditions closely simulating fibroids. This same asymmetry is very common and very easily detectable after expulsion of the placenta. Not infrequently I was convinced that fibroids were present when really there were none.

As the hours pass during uterine effort, the true character of the pains is revealed by an examination of the cervix. The effect upon the cervix is surprisingly disappointing both in point of effacement and of dilatation. So the process goes on. Later the uninitiated may be startled by the development of a very unnatural shape of the uterus. It usually consists of two or three large segments with ridges between. The commonest is the bilobed type, not infrequently the bladder is full, and adds to the confusing appearance. This is due to a spasm of the circular fibres of the uterus. This lately was clearly demonstrated at Caesarian section in the early state of anesthesia. In this case I was able to outline the contours of the uterus with the hand and was able to feel the contraction rings which often affects only a part of the circumference of the uterus at any level. The spaces between the contraction rings were partially relaxed and bulged correspondingly. The condition in bad cases is very disturbing to the obstetrician's equanimity.

As the case progresses the bladder becomes functionally ineffective and re-

tention with its distorting effect upon the abdomen becomes pronounced. Still later the colon begins to distend with gas. It is impossible to tell whether the distension will affect the cecum or the sigmoid. In the majority of cases the sigmoid is involved and slowly distends, often to reach the size of a football. This displaces the uterus to the opposite side of the abdomen, forcing the long axis of the fetus to take a diagonal out of the long axis of the mother. When the uterus now contracts, the bowel goes into spasm at the same time giving the abdomen an appearance of mounds and valleys. Still later the stomach becomes distended in a manner similar to the large bowel and eventually vomiting sets in, and quantities of blackish fluid are cast off. If the membranes had ruptured early the amniotic cavity usually becomes infected and the fluid which escapes when the head is displaced by forceps or other means is usually very fetid. At this stage the pulse and temperature begin to rise and when this occurs one or two conditions develop. 1) The "pains" frequently die down and disappear completely, or 2) the uterine effort changes, becomes effective and ends the labour spontaneously. Following prolonged vomiting not infrequently catarrhal jaundice may set in after the labour is ended, or a very distressing fetid diarrhea may follow the bowel stasis of pregnancy.

Such is the course of the severe type of primary inertia. Naturally there are all grades. The severe cases will tax the ingenuity of the obstetrician to the utmost. The case ends in one of several ways. Let me explain the development of these various phases.

#### THE EFFECT OF PRIMARY INERTIA UPON THE FETUS

Uteri whose muscle does not function normally are prone to pass into a state of prolonged spasm. This has one of two effects upon the fetus. 1) Either it produces a stage of asphyxiation to the degree that fetal peristalsis and sphincter relaxation produce passage of a large amount of meconium, the spasm eventually passing off and the fetus recovering; or 2) the spasm may continue until the child succumbs *in utero*.

Aspiration of infected amniotic fluid may lead to aspiration pneumonia and sinus complication in the days immediately after delivery, and impetigo is not an uncommon sequel.

#### THE PROGRESS OF THE LATE FIRST AND THE SECOND STAGE

Nearly all these cases end in a more or less difficult forceps upon an exhausted mother and a very tired fetus. Interference may be necessary, even imperative, before the cervix has completely dilated.

Moreover, many of the cases remain persistent occipito-posterior for the following definite reasons.

1. The descending presenting part in labour must strike the pelvic floor with sufficient force and rapidity to make a definite impression upon the levator. If, as in most of these cases the advance is so slow the levator muscles are not awakened into activity to elicit the efforts of the second stage. The condition is similar to approaching an instrument slowly to any tactile surface. If the

approach is unduly prolonged there will not be any sensation of contact. The pelvic floor must suffer a certain definite conscious foreign contact to elicit its counteraction. This is absent in most cases of prolonged inertia. Consequently the patient does not know when the second stage is on and has no stimulus to act, so that the fetal head usually remains fixed in the diagonal in which it engaged at the pelvic brim, owing to slow descent and lack of levator resentment.

2. Another important factor in lack of normal rotation is found in lack of fetal tone. A fetus that is tired or exhausted, one that has suffered repeated attacks of partial or grave asphyxia, loses its tone. This distinction between a normal and abnormal tone can be appreciated by the feel of a normal child and one in a state of asphyxia pallida. But what has fetal tone to do with rotation? It is this. Any sensitive accoucheur can feel when the forceps are applied to a normal fetus the movement imparted to the forceps by the fetus in trying to help itself out of its predicament. It is one of the most comforting feelings to appreciate fetal movement of the head upon the body during forceps delivery. When not present I am conscious of an anxiety even in spite of a normal fetal heart rate, and my misgivings are seldom misplaced. Dozens of times I have demonstrated to my student classes the movement imparted to the forceps by forceful fetal action. On the other hand, this sensation is seldom or never obtained if, by chance, morphine or heroin had been given within two hours before delivery.

3. When the membranes have been ruptured in these cases of prolonged labour due to inertia, there develops an inordinately large and deep caput. It is generally taught that a caput is nature's substitute for the bag of waters and and that it assists in the dilatation of the cervix. That is a gross error. In a paper which appeared in the *Journal of Obstetrics and Gynaecology, British Empire*, 40: 1021, 1933, I outlined the function of the caput and showed clearly that not only is it not an aid to dilatation, but on the contrary, it is a direct hindrance to normal rotation. Let me explain.

The caput is not an aid to cervical dilatation. If we study the physiology of the caput we realize that it is merely an unsupported part of the scalp, and is formed by a pressure ring of the cervix or vulva, causing an impediment to free circulation of the blood. The arteries entering this area, owing to their higher blood pressure and thick walls, can bring blood into this unsupported area of the head, but the blood, once in, cannot so easily get out through the veins owing to their thinner walls and low blood pressure. The consequence is that the caput is proportionate in depth to the strength and duration of the labour pains and is proportionate in size to the cervical dilatation. Since there can be no caput without a cervical pressure ring, the ring becomes the cause of the caput, and the caput follows, but does not aid, the dilatation. This is the caput of the first stage of labour. Normally it is eccentric to the midline of the head, situated over one of the lateral bones of the head.

When such a first stage caput now descends into the second stage, it naturally tends to occupy the axis of the pelvis, but the caput is lateral to the mid antero-posterior plane of the head which must come into the axis of the pelvis. Con-

sequently the forces of the second stages of labour must be sufficient to displace the caput out of the axis of the pelvis to a lateral position. This can be demonstrated in two different ways. Some fetal heads have two caputs, one a cervical, the other a vulvar. They are quite separate, and are formed first by the cervix, then when rotation has taken place and the caput has been displaced laterally, another caput will form if undue resistance is encountered at the vulva. But the delaying effect of the caput can be convincingly demonstrated by the application of forceps. I deliver all my cases by prophylactic forceps, and in these cases where rotation has been completed, the caput lies outside the line of the midpelvis and when the forceps are applied the caput lies closely under one blade and remote from the other. When, on the other hand, rotation is arrested, the caput occupies the axis of the pelvis.

#### THE CAUSES OF NEURO-MUSCULAR DYSTROPHY

It is now generally conceded, I think, that these neuro-muscular dystrophies are the result of abnormal metabolism in the autonomic nervous system or in the muscles that they supply. It has always been a debated point whether any disease affecting muscles is primarily a disease of the nerve ending of that muscle, or of the muscle fibre itself. The distinction is not essential for our purpose.

Let us examine the construction of the uterine musculature. It has been frequently demonstrated that the uterus is made up of two distinct parts, the upper and lower uterine segments. It is now generally taught that the former is active and the latter passive. Let us inquire more closely into this phenomenon. The uterus is made up of several muscular layers. It is generally agreed that there are three of these, the outer longitudinal, the middle criss-cross, and the inner circular. These have, we assume, separate and divers functions. The longitudinal which spread from base to fundus, constitute, when in operation, the expulsive force of labour. The criss-cross are the "stop-cocks" on the blood vessels, and the circular fibres are tonic fibres which maintain uterine rotundity and cylindrical shape for the pursuits of labour. I need not go into the details of these distributions. They have been outlined by many competent authors.

The nervous systems which supply these structures demand a fuller description.

It is well known that the uterus as a whole is supplied with three activating and controlling systems. There is the automatic system of ganglia in the uterus, whereby the uterus undergoes a rhythmic contraction similar to that of the heart. This automatic potentiality can be maintained even when the uterus is severed from the body. Acting upon this automatic system is the autonomic system, whose influences are as activators or inhibitors. Kuntz states "In view of experimental data available at present it may be assumed that the uterine musculature, like other smooth muscle, possesses the inherent capacity to undergo rhythmic contractions; but under conditions of normal innervation the activity of the musculature is subject to both motor and inhibitory nervous influences, which may be reflex or of central nervous origin."

From the above statement and from observations we can state categorically that there is a basic uterine motor with an accessory activator and inhibitor. The parasympathetic and sympathetic systems supply the activating and inhibitory principles respectively. Johnston, in Gray's Anatomy wrote, "The autonomic system can be subdivided into two more or less complementary parts, viz: the parasympathetic and the sympathetic systems, partly on anatomical, partly on physiological and partly on pharmacological grounds. Anatomically it can be demonstrated that most of the viscera of the body receive their nerve supply from two sources, one source being the parasympathetic system, and the other the sympathetic system. Physiologically it can be shown, for most of these viscera, that the influences of these two systems are antagonistic to one another. Pharmacologically, it has been found that certain poisons which paralyse the sympathetic nerve endings do not affect the parasympathetic nerves, and vice versa. In addition, the sympathetic system comprises two gangliated trunks, together with their communications and their branches of distribution and subsiding ganglia, so that it constitutes a definite anatomical entity, whereas the parasympathetic system utilises certain of the cerebral and certain of the sacral spinal nerves as its pathways, and does not lend itself readily for anatomical demonstration." It would prolong this article unduly to go into the details of the experimental work that led up to the above facts. It may be stated that the automatic action of the uterus can operate without the autonomic system, but that the latter, by any over-action, may introduce abnormal modifications into a physiological action. Whitehouse and Featherstone wrote, "The sympathetic stimuli appear to be definitely inhibitory to the longitudinal fibres of the uterus and motor to the circular fibres, and, acting in antagonism to these stimuli, the influence of the spinal cord (parasympathetic) is motor to the longitudinal fibres and inhibitory to the circular fibres."

In the British Medical Journal of 1923, Whitehouse and Featherstone wrote, "1. The nervous mechanism controlling the uterus is constituted by three systems: 1) Local; 2) Sympathetic; 3) Lumbosacral Autonomic (parasympathetic).

2. The 'Local' system is capable of producing rhythmic uterine contractions, and is independent of the sympathetic and autonomic systems in common with other voluntary muscle.

3. The sympathetic stimuli are motor to the circular fibres and inhibitory to the longitudinal bundles.

4. The lumbar cord (parasympathetic) stimuli are motor to the longitudinal and inhibitory to the circular fibres.

5. Both para- and sympathetic stimuli are controlled by higher centers in the medulla and possibly the cortex, but are capable of acting independently of the same.

6. Reflexes, both (a) autonomic (parasympathetic) and (b) sympathetic, are probably important factors in normal uterine contraction.

7. Uterine contractions, to be effective, depend equally upon the integrity and correctly adjusted balance of autonomic (parasympathetic) and sympathetic impulses.

Disturbance of either, whether in the direction of augmentation or diminution, will interfere with the normal course of labour."

It will be readily seen from the above that the term "autonomic" is used by Whitehouse and Featherstone to indicate the parasympathetic system, whereas Johnston, in Gray's Anatomy, uses the term "autonomic" to cover the whole of the secondary nervous system including both the sympathetic and the parasympathetic systems. The parathentic corrections in the above quotation are by myself to avoid any confusion of terms.

It is necessary to emphasize the statements above that the autonomic system, though autonomic in its action, is under the influence of the medullary and intercranial systems, and therefore is subject to modification by any strong cerebral stimulus, whether emotional or traumatic. We know the influence of the assurance given the patient by the arrival of the doctor, or the arrest of pains by any sudden change of circumstances during labour. But we are apt to forget that, in the vast majority of cases, the autonomic nervous system is one of the normal means of transmitting the effects of the endocrines to their ultimate destination and operation. The recognition of this fact makes it clear that any abnormal change in the autonomic nervous systems, whether it be endocrinological, chemical, emotional or metabolic, must upset the delicate balance of its normally acting and counteracting forces and change the effect correspondingly.

There is room here for a grave misapprehension of uterine action. It revolves about the terms "normal tonus" and "relaxation." There is a vast difference between spastic tonus, normal tonus and relaxation. One can conceive of a normal tone as the outcome of a continuous stream of vivifying impulses which are generated in the centers of production and are transmitted along the nerve paths to the muscular elements. It is equally easy to conceive of this tone being exaggerated into an abnormal spastic state by the increase of its stimuli regardless of their origin. But it is not so easy to conceive a relaxation. Theoretically it may arise from a lack of stimulation or the normal tonus may be overcome by an opposing muscular force. Let me try to explain the difficulties that my rationalizations encounter.

It has been my fortune to find, on several occasions, cervixes that are fully dilated, yet have never had either a fetal pole or a bag of waters to act as a dilator. How is such a state of affairs brought about? Let me quote a case to illustrate the point. I was called by one of my assistants to see a multipara with a prolapsed arm. The membranes had ruptured at the onset of labour. She had a large flaccid pendulous abdomen in which the uterus was prolapsed anteriorly. So much so that the baby occupied the overly pendulous atonic fundus. The axis of the uterus pointed upward instead of downward. The consequence was that the fetus never engaged. The arm prolapsed and when I saw her, Bandl's ring was tightly contracted about the upper arm; but, and this is the interesting observation, the cervix was completely dilated to the degree that obtains at the end of a first stage. Yet the waters had gone at the onset and there was no dilator except a hand and forearm. The baby was dead and with anesthesia to a depth that approached death it was impossible to

expand that ring, and morcellation of the dead fetus was done with the utmost difficulty through the small aperture in Bandl's ring. This is but one of several such observations of a completely dilated cervix without the advantage of a fetal pole or of a bag of waters to act as an obturator. The question at once arises: "What is the dilating force if there is no downward thrusting object?" If my observations are correct, and I may add they have been corroborated by some of my colleagues, I repeat, if my observations are correct and my interpretation of them rational, then the inference is that under certain conditions the circular fibres of the lower uterine segment may dilate completely under the pull of the longitudinal fibres of the uterus. That the circular fibres of the lower uterine segment, vagina and perineum may relax completely by withdrawing the normal tonus-stimulus is observed in the extreme relaxation of the cervix, vagina and vulva under caudal anesthesia. Under these circumstances of anesthesia, repair of the torn cervix and of an episiotomy wound requires almost a new technique, owing to the absence of the normal tonus to which we had become so accustomed that, when faced with this new form of relaxation, we have to readjust our technique. We do not obtain this relaxation in ordinary spinal anesthesia. This is a potent argument in favor of the concept that the seat of the parasympathetic is in the lumbo-sacral region, and that its nerve endings are directly affected by the caudal anesthesia, so that its activating force is negated.

#### TREATMENT

It will be readily seen that the causes which may bring about autonomic imbalance are manifold. It is therefore futile to expect that any one specific could cover anything but a fraction of the cases. Theoretically, the autonomic imbalance, moreover, may be due to overstimulation of one part of the system from the central nervous system, or from over-excitations and hyperreceptivity of the autonomic nerves themselves. Equally, it may be argued, that ineffective responses of the autonomic nervous system may be produced by malnutrition, avitaminosis, drugs, etc. In any case, change in balance of the two autonomic systems of nerves creates an imbalance and gives one of the two systems preponderant force over the other, with a corresponding maladjustment of the effects that their functions subtend.

I shall not dwell upon the effect of strong emotions upon the course of labour. This subject is too well known to the obstetrician to require amplification. Like all common knowledge, the matter is only too casually considered.

I want to concentrate the attention chiefly upon the effects of calcium and phosphorus deficiencies during pregnancy and labour.

My attention was directed along this line of treatment by two instances of prostration and cramps after prolonged swimming. These two cases did not respond to any form of treatment until calcium gluconate was used intravenously when, after the first injection, the recovery was really astonishing. Later I began to administer calcium to all my patients who suffered from muscular spasm during pregnancy. The response in certain cases was equally prompt,

but not always successful. Calcium was then given in combination with vitamin D to increase its absorption. Since the administration of this combination I have had very few cases in which there is not a prompt response. In all my cases of pregnancy a capsule of Calcium A, is ordered daily as soon as vomiting of pregnancy, if present, permits of its tolerance. The cod liver oil which is present is usually well borne except during the weeks of pregnancy nausea. From the fifth month on, the capsules are increased to two daily and from the seventh month on, three daily are administered. Muscular cramps disappear almost completely except in a few cases, when the dose has to be increased up to 7 or 8 capsules daily for a time.

Owing to the efficacy of this treatment in abnormal neuromuscular function, I was tempted in a marked case of primary inertia to employ the calcium vitamin D treatment. Two injections of calcium gluconate intravenously and two intramuscular injections of vitamin D were employed at 2 hour intervals. The case was about one-third dilated at the time of examination, though she had been in labour 38 hours when I was called in consultation. She delivered herself spontaneously in a little over four hours. This treatment has given prompt results in a goodly percentage of cases. But it has been disappointing in others. It is of service, of course, only in the cases which come under observation when in labour. Since the introduction of the Calcium A treatment, primary inertia cases have very appreciably diminished in my practice, and it has been found that labour pains are more rhythmic, more effective and the intervals much freer from distress, owing to complete relaxation and freedom from spasm. The results, in the vast number of cases, are so striking that the internes wondered why, because I had not made known to anyone the experiment that was being carried out. Now the treatment is widespread among those who know.

A percentage of cases do not respond. This should not cause any wonder, because the causes of dystocia due to neuromuscular defects are multiple. But whatever the causes, whether they be of central nerve origin or of local origin in the pelvis, I feel that the effects of these must be diminished by coming into contact with a normally fed and well balanced neuro-muscular structure. Primary inertia uteri is a relative disease. Only the severest cases are sufficiently obtrusive to permit diagnosis. They are usually accepted as merely undue lower segment resistance. These are the ones that have appreciably diminished. I have been particularly impressed with the ease with which many elderly primiparas completed their labour when I had anticipated exhausting extension of the labour-time. Particularly is the interval relief astonishing and it has been ascertained, just as one would expect, that the amount of sedative necessary is considerably reduced.

One must here add a word of caution in estimating one's results. Calcium and its adjuvant vitamin D are particularly effective in establishing the balance between upper and lower uterine segments, but their effect upon the vaginal muscles, though perhaps as effective, is not so spectacular, because in this area there is but small, if any, expulsive force, so that the action of the calcium would be to promote easier expansion of the vaginal circular fibres. But in many

women, even young ones, the vulvar development may have been arrested, even though the upper sex organs may have reached normal growth. One frequently sees in gynecological cases this disparity between the upper and lower organs of generation, and this disparity is carried over into the pregnant state. So calcium administration, though it may hasten the first stage of labour, may find difficulty in the second stage in keeping up its standard of time and effect.

#### CONCLUSIONS

The human uterus is composed of longitudinal, circular and criss-cross fibres. The longitudinal fibres have to do with expulsive efforts; the circular fibres control uterine tone in maintaining the proper axis of the fetus, and maintain constructing sphincteric action; the criss-cross fibres control blood supply. The three layers are not clean cut, but intermix to a degree.

The uterine musculature is activated by three sets of nerve cells. There is the ganglionic set which gives the uterus its power of rhythmic automatic contractions; there is the parasympathetic derived from the lumbo-sacral plexus whose stimuli increase the longitudinal expulsive efforts of the upper segment and inhibit the circular constricting fibres; and the sympathetic thoracico-lumbar system which activates the circular fibres and inhibit the longitudinal. Normal labour pains, other things being normal, depend to a great degree upon the proper balance of these stimuli. Though these uterine intrinsic structures are self-acting, they are under the control of the central nervous system. They are, therefore, subject to change due to stimuli from the central nervous system, but also subject to change owing to metabolic, chemical, endocrinologic or other form of internal derangement which may abnormally enhance or diminish their action, thereby upsetting the normal balance between the various systems.

Any emotional stimulus, such as fear, pain, anger, starvation, etc., may introduce cerebral transmissions which may greatly modify the normal course of labour by upsetting the balance between expulsive and retentive forces. Muscular cramps of skeletal and involuntary muscle bundles are of the nature of malnutrition and can be arrested by appropriate treatment.

Imbalance in the neuro-muscular mechanism of the uterus is one of the causes of primary inertia uteri.

One of the causes of this imbalance is found in a deficiency of calcium metabolism. That the administration of this drug does not relieve all the cases of primary inertia is evidence that the causes of inertia are multiple.

The preparation of calcium and vitamin D was that prepared by Ayerst, McKenna & Harrison, entitled "Calcium A."

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## THE TRANSVERSE SUPRAPUBIC INCISION IN GYNECOLOGIC OPERATIONS

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This may appear a trite subject, nevertheless it is the more or less accessory procedures in surgery that should be given occasional consideration, even if their results are based merely on the experiences of an individual operator. Among these is the abdominal incision as applied in gynecologic surgery. The appropriate location for an approach to the pelvic organs through the abdominal wall and the manner of suturing have served as topics for innumerable discussions and many operators each have claimed for their own procedures the maximum of good healing qualities and postoperative safety.

The most common approach has been the suprapubic median incision through skin, fascia and peritoneum. Modifications of this have included a skin incision over the right or left rectus with displacement of the muscle, so that when the incision is closed the restored muscle would be interposed under the fascial suture, possibly preventing a future hernia. Aside from plain catgut suture of the peritoneal layer, a more delayed absorption of chromic gut prompted its use in the fascia. Tension sutures of various non-absorbable material were deemed necessary for the skin, supplemented or not in many instances with the still popular Michel's clips. And one who did not employ this supposedly and invariably safe method was regarded as a heretic and dire predictions were made of an insecure closing, with its probable failure to avoid evisceration or later hernia.

Contrary to these beliefs I have always felt that good and firm union depended not only on healing unencumbered with non-absorbable suture material, but also on careful, gentle retraction and on the location of the wound. The latter should not only be firm, it should present a minimum of scarring evident to the eye. Women are no longer proud of abdominal scars or their number, and they are apt to judge the surgeon's skill by the subsequent appearance of the wound. Naturally there are instances in which large and ugly scars are unavoidable but the size and distortion found in so many cases appear inexcusable.

I have become impressed through the years with the many advantages of what is generally designated as the Pfannenstiel incision. While its execution may take more time and exposure of the abdominal contents may be more limited, its advantages become evident to any one who will employ it consistently.

Detailed descriptions of the steps in carrying out the opening of the lower abdomen by a transverse incision may appear superfluous yet there are certain points to which attention may be called

1. Skin incision. This need not be made, as generally directed, along the pubic hair line which is subject to certain variations but can be made in an abdominal fold at a higher level, especially where removal of pelvic tumors is

contemplated or for other procedures. The line between the anterior superior spines provides the most satisfactory anatomic landmark.

2. Fascial incision. This likewise should be transverse and directly under the skin incision. After the fascial layer has been separated from the underlying muscles, the edges should be sutured to large, wet, protective gauze pads.

3. Separation of recti muscles can be carried in the median line and the pyri-formis separated if it is well developed and displaced to one side or cut through and sutured later. Usually it is not necessary to free the peritoneal layer but it should be well exposed.

4. The peritoneum is incised in the median line with the usual precautions as to adhesions and bladder.

5. Retraction of the wound edges should be done preferably with the assistant's fingers or hand-held small retractors. Mechanical, permanent retraction with special devices is rarely necessary and, in my belief, results frequently in trauma of the abdominal wall, which interferes with wound healing and constitutes a factor in the production of postoperative pain. Exploration of the pelvis can be done manually without difficulty and the internal genitalia brought into view. The appendiceal region should be explored and if removal of the organ is necessary, this can be postponed until the pelvic surgery is completed,—a guide ligature may be placed around the base temporarily.

In the event that tumors are encountered which are too large for ready delivery through the wound, their size may be reduced by appropriate measures. As a general rule if a new growth reaches considerably above the umbilicus and is solid in character, a median rather than a transverse incision should have been chosen. The ordinary hysterectomies, either supracervical or complete, tubal and ovarian surgery, and a variety of uterine suspension operations, all can be done without difficulty through this incision. The entire abdominal contents can be explored with the hand. If an attack on the gall bladder is found necessary it had better be done through an appropriately placed incision. The Trendelenburg position and the gauze filled rubber pads will serve to displace the intestinal coils and gauze strip or roller packing for this purpose is undesirable and rarely necessary.

6. Closure. Proper suture of the abdominal wound after the pelvic surgery has been completed is important. The peritoneal incision is closed with a continuous suture of #1 plain gut avoiding puckering. The fascia is likewise sutured with plain gut #2, interrupted or continuous, and the skin wound with a subcuticular suture of fine catgut or celloidin silk or nylon. Naturally all bleeding must be completely controlled, several interrupted catgut sutures in the subcutaneous fat may be necessary.

I have rarely resorted to the so-called "tension sutures" of non-absorbable material or the Michel skin clips. A firm adhesive plaster strapping is applied over dry gauze, leaving an intermediary "air space" and the first dressing is done on the fourth or fifth day.

The evaluation of any technical procedure by an individual operator depends on the results achieved. His estimate may or may not be of interest to his col-

leagues. My own satisfaction with this type of abdominal incision and wound handling which I have employed in suitable cases since 1919, has prompted this presentation. I say suitable cases, because the transverse suprapubic incision is not always applicable, as must be evident. The data here presented are based on the records of private patients only, upon whom I have had opportunities to do personal follow-up examinations. Hospital service cases are not included. From a recent study of the histories, the following data are available:

<i>Operations (260)</i>	
<i>Uterine Suspensions—</i>	
Kelly.....	8
Baldy-Webster.....	33
Coffey.....	31
Hysterotomies (abortions).....	9
Hysterectomies.....	50
Salpingo-oophorectomies, including removal of cysts.....	102
Appendectomies.....	27
Total.....	260
<i>Hospitals</i>	
New York Lying-In.....	14 cases
Woman's.....	96 cases
Booth Memorial.....	64 cases
Scattered.....	7 cases
Total (1919 to 1943).....	181 cases

Among these 181 cases there were five instances in which serous drainage occurred (Class B, Woman's Hospital Classification) and one with a moderate degree of infection. All of these healed satisfactorily. In one case a hematoma of considerable size resulted from a subcutaneous hemorrhage. This necessitated evacuation and packing but the wound healed promptly. In no case did a post-operative hernia occur. All of the patients were seen at varying periods and had any difficulties developed subsequently I feel quite certain that I would have been informed.

Although my personal record of operations may not compare in number with those of others, my experience with the procedure is sufficient to warrant the conclusion, in my opinion, that the transverse suprapubic incision, manner of wound handling and closure with absorbable suture material as described, constitute the most satisfactory approach for pelvic gynecologic surgery.

## CORONARY THROMBOSIS: PROPOSED TREATMENT BY HIRUDIN

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*This paper is contributed to the Anniversary Volume honoring Dr. Vineberg after his many years of conscientious, scientific and skillful service to The Mount Sinai Hospital where I have followed his career with interest and admiration.*

*The observations and the suggestion presented have no direct connection with gynecology nor, strictly speaking, with surgery; though there is no branch of our profession in which the heart and its disorders may not become the deciding factor in the treatment of the patient.*

*It is my sincere hope that Dr. Vineberg and the many who peruse the pages of this volume may realize that I have given them something for reflection.*

In early thrombophlebitis of the lower extremity the application of leeches to the neighboring skin, not directly over the vessel, will usually be followed by amazingly rapid and complete recovery, provided that the bleeding from the bites is checked when the animal has relaxed its hold. The anticoagulant, hirudin, is thus retained in the body.

Instead of fixation of the extremity and long rest in bed with only a small percentage of complete cures the patient may be up in a chair within three days and apparently well in less than a week, palpable swelling and all pain having disappeared.

French surgeons have long treated thrombophlebitis by leeching although no mention has been made of hemostasis of the bitten region.

When the condition has followed operation on the abdomen with extension into the pelvic veins this therapy was especially efficient. It was discontinued a few years ago because of the fear of pulmonary embolism by a clot loosened from the upper part of the diseased vein.

Whether or not this accident is more common after leeching has not, however, been proved since embolism may occur during simple rest-treatment. Its mortality is high.

Trendelenburg devised a method for extracting the clot from the pulmonary artery or its branches by surgical approach through the anterior chest wall. Successes, though not numerous, have been reported by other operators (1).

Thrombosis of the coronary arteries of the heart is rapidly increasing. I am informed by Dr. Louis I. Dublin, statistician and third vice-president of the Metropolitan Life Insurance Company, that it now ranks third in the causes of death, exceeded only by cancer and by other disorders of the heart. It is seen most frequently in males who have reached the age of fifty and who have been engaged in occupations involving executive responsibility.

Coronary thrombosis is, apparently, preceded by a roughening of the tunica intima and may finally fill the vascular lumen though it begins peripherally.

Plugging of the smaller vessels near their distal termination may not interrupt cardiac pulsation sufficiently to cause death and, after long rest-treatment the proximal branches may dilate until the loss of circulation in the heart-muscle has been compensated. Life, apparently normal, may then go on for years.

Since there is no direct connection with the pulmonary circulation, embolism does not occur and the principal danger is that thrombi may extend into the proximal coronary arteries until the cardiac circulation is fatally compromised.

The only treatment has been by rest and analgesics—keeping the patient alive until proximal coronaries have enlarged sufficiently to make up for the occluded ones.

In the Proceedings of the Staff Meetings of the Mayo Clinic, Vol. 17, May 20, 1942 there is a symposium on coronary disease. The article on Treatment and Management was contributed by H. L. Smith, who advised only drugs for analgesia and sedation.

Various methods other than rest have been attempted but with little or no beneficial results. The one most often employed in the past has been blood-letting in some form; until very recently leeches were used. The animal drops off when replete with rarely more than an ounce and a half of blood but hemorrhage will often continue long afterward.

In order that the leech-poison and anticoagulant, hirudin, may be retained in the patient's body the flow from the leech-bite must be stanchd. This can be easily accomplished by pressure of the finger moistened with adrenalin. Cases have been reported in the old literature of fatal bleeding in children following leech-bites.

I can find no mention of the employment of pure hirudin therapeutically in human diseases accompanied by or caused by *intravascular* coagulation but experiments are in progress.\* Meanwhile, deaths from coronary thrombosis continue to multiply.

Other substances which may inhibit coagulation but which do not dissolve clots are heparin and a coumarin product from sweet clover.\*\* Perhaps the vampire bat may secrete a substance which prevents coagulation since animals of large size may fatally bleed following the infliction of the small wound which is made by the bat.

Referring to the therapy of heparin I find no mention of its use in coronary thrombosis in the latest books on therapeutics (2) nor in works on pharmacology (3). No mention is made of dissolving clots but merely preventing their formation. And, let me repeat, leeching, (hirudin) does dissolve unorganized intravascular coagula.

The investigation of heparin continues (4) but thus far it has nothing to do with our subject.

\* Burroughs Wellcome & Co. have this in stock.

\*\* Dicoumarin.

On going over the matter with a number of physicians I have found them interested but not cooperative although the treatment need not interfere with the usual bed-rest.

Surgeons seem to be more receptive as may be exemplified by a letter from Dr. Alton Ochsner of Tulane University who permits me to quote him:

"I have tried to get my medical friends interested in using leeches in coronary thrombosis and have told them that if I ever develop it, I want them to cover me with leeches because I am thoroughly convinced that the hirudin is a potent drug and would be of benefit in such a case."

#### CONCLUSION

This subject is here presented in the hope that general practitioners may become curious enough to give the method a trial without necessarily discontinuing the rest therapy.

If it can do no harm and may turn out to be an advance in the care of this rapidly increasing disease it would be unfortunate to leave the therapeutic experiment to future generations.

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## A FORGOTTEN MEDICAL WORTHY—DR. HENRY JULES GARRIGUES

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It is a happy coincidence that a medical man is able to contribute a few pages to the history of obstetrics to his old friend, Dr. Hiram N. Vineberg.

The centenary of the publication of Oliver Wendell Holmes' epochal essay "On the Contagiousness of Puerperal Fever" was celebrated in this City only a few months ago (February, 1943). It attracted a large gathering of over a thousand people who were interested in maternal health and child welfare. A symposium and a conference was followed by an evening session at the Academy of Medicine.

The local press had long laudatory accounts of all of the proceedings of the sessions and especially had referred to the papers of Dr. Guttmacher of Johns Hopkins and Dr. Watson of the Sloane Maternity Hospital. Both of them had discussed the history of the past century's development in the conquest of puerperal fever, and both of these speakers emphasized the gains in this city during the past ten years from the times of Holmes and Semmelweis.

I was especially interested in listening to some of the papers, not from the standpoint of an obstetrician, but for a personal reason. This took me as far back as 1887, when I was an interne at the old Charity Hospital on Blackwell Island, now known as the City Hospital on Welfare Island. At that time the rotation of the services had included six weeks' periods at the well known New York Maternity Hospital, then either the only or the best service in the city.

Among its attending surgeons was the outstanding figure in obstetrics of that period, Henry J. Garrigues. As puerperal sepsis was banished from his wards his life saving work became well known and accepted in this country.

Therefore, it was a great surprise to me that neither the name nor the work of Garrigues were even mentioned at those meetings. Those who lived at that period appreciated his work which had conquered the unbelievably large morbidity and the mortality of puerperal sepsis in hospital and private practice sixty years ago.

Those few survivors also may recall and remember the ridicule of the new antisepsis in midwifery. The chief of the staff of the New York Maternity Hospital had not even tried it and had stated that it was not feasible to carry it out. His routine consisted of nothing more than washing the hands with soap and a two per cent carbolic acid solution, and vaginal douches of the same solution three times daily in every confined woman and oftener when the temperature ran high. No other measure of any kind was employed. As the result of this method in the first nine months (January to September) of 1883, there were 345 deliveries of which 30 women died, while in the rest the morbidity of sepsis was enormous. In one month of that period, 10 women (25 per cent) died, while the survivors were so sick they had escaped a fatal issue most miserably.

At that time, October 1, the rotation of the service brought Garrigues into charge. He was appalled by the frightful conditions; he studied and formulated his plans to drive out the pestilence. At once they were carried into effect. There was a broad comprehension of the principles of antisepsis in every detail and complete isolation of pavilions was instituted. It was brilliant in its achievement and it had far reaching influence on the practice of obstetrics.

He proved to be the man superior to the emergency and the pestilence and its terrors fled into the night. In his first report of those three months, September to December, 1883, he wrote, "As if by magic all trouble has disappeared, 97 women have been delivered since its introduction, not even one has died, and scarcely with any inflammatory lesions and only three had any rises of temperature. The pavilions are scarcely recognized whereas we have been accustomed to offensive odors; feverish prostrated and despairing patients; overworked and despondent doctors. The air is pure, the women look well, the temperatures are normal, the nurses cheerful and the doctors happy."

This antisepsis midwifery of Garrigues with its brilliant results was continued when I was an interne in 1887 in this maternity hospital when puerperal sepsis was unknown for four years in its wards. As the pavilions were quarantined from the wards of the Charity Hospital, these days were not too busy for me with other work. As a result I had the chance to study old records in huge bound volumes of the years of "the old era," and I still recall those melancholy pages of many horrible past epidemics with the red headings of those who had died of sepsis.

There is no need for a description of the details of Garrigues' treatment, nor is it necessary to discuss the old question of puerperal sepsis of that period, since they are not in my province as a medical man. Also there is nothing especially new in Garrigues' method which has been known for a long time. What was novel was the coordination of antisepsis, quarantine, the most careful cleanliness, the attention to minute details of air, plumbing, floors of the building, linens, etc.

To quote Osler, who said of Holmes: "As Sidney Smith said, it is not the man who first says a thing; but it is he who says it so long, so loudly that he compels men to hear him. It is to him (Dr. Holmes) that the credit of insisting upon the truth of the contagiousness of puerperal fever belongs."

The same words may be paraphrased for the work of Garrigues in clearing the atmosphere of the aseptic conditions in midwifery sixty years ago.

Briefly about the relations of Garrigues to Holmes. Garrigues was a strong believer in Semmelweiss and, so far as I can remember in my early days, Holmes' influence had very little effect on medical affairs. He was famous only from the standpoint of literature, less so as an obstetrician; otherwise he was known as a professor of anatomy.

Dr. Reginald Fitz in his delightful paper at the recent centenary meeting of the Academy of Medicine on "My Doctor Holmes" referred to the well known fact that at the large dinner in this city in 1883 which had been tendered to Holmes, not a word had been said of his well known essay on puerperal fever.

Holmes himself had stated that it had been too unfortunate that he had published it in an unknown medical magazine of a limited circulation. Had he sent it to the American Journal of the Medical Sciences, which was very well known even at that time, the medical profession would have known of his views on puerperal sepsis.

Also there was the exchange of letters in 1889 between Holmes and Osler. In Osler's paper on Holmes in the Johns Hopkins Bulletin, October 1894, may be quoted the following: "I think I will not answer the question you have given to me—I think oftenest of the 'Chambered Nautilus' which is a favorite of mine, though I wrote it myself. The essay comes up at long intervals . . . There is more selfish pleasure to be had about the poem,—perhaps the nobler satisfaction from the less saving labor."

About Garrigues himself, I remember him as a tall, reserved man with definite views spoken in a somewhat foreign accent. He was kind to his staff and helped them in every way.

A search through the up to date standard national and local biographical dictionaries has been a failure and disclosed that his name and his work are absolutely unknown to the present generation. He had outlived his times and when he died in 1913 at the age of 82 years the New York medical press had only short obituaries about him. The only notice taken of his death was a memorial address before the Obstetrical Society by Brooks Wells who had been his colleague and pupil.

Henry Jules Garrigues was born in Copenhagen in 1831 and he was graduated from the University of Copenhagen receiving a B.A. degree in 1850 and later in 1863 an M.A. degree. He had studied medicine for four years, but he had given it up because of poor health and had travelled in Europe. He returned as a professor of French at the Academy of Copenhagen. He then resumed the study of medicine and was graduated in 1869 when he was 38 years of age.

After practicing in Copenhagen for six years he emigrated to America and settled in Brooklyn as a doctor. Later in 1875 he moved to New York City and lived there for many years.

His first hospital appointment was that of gynecologist in the German Dispensary in 1879. In 1881 he became obstetrical surgeon to the New York Maternity Hospital and also to the New York Infant Asylum. In 1885 he became gynecologist to the German Hospital, and in 1886, Professor of Obstetrics in the New York Post-Graduate School. In 1907 he was elected an honorary fellow of the American Gynecological Association and in 1902 honorary fellow of the Obstetrical Society of Edinburgh.

He was a voluminous contributor to the journals and wrote text books on his specialties. The "Practical Guide of Antiseptic Midwifery" in 1886 and the "Diseases of Women" went into several editions.

When he retired from practice he moved to Troyon in North Carolina. There he became especially interested in Esperanto and he wrote about it. He died in 1913 and his tombstone carries an inscription which includes the sentence "On October 1883 he introduced antiseptic obstetrics in America."

Great were the difficulties which Garrigues encountered on every side with the ridicule of his rigid measures by the medical profession. That period was the dawn of today's modern medicine in which the pioneers struggled to hew their hard roads. Even in that era Pasteur frequently had to repeat his demonstrations to the unbelieving scientific and medical world before it was conquered.

Today those crude times of achievements and contradictions cannot readily be understood. As an example may be cited Lilienthal's graphic picture of a well known, skillful surgeon of The Mount Sinai Hospital strapping his scalpel on the sole of his boot.

I, too, may add some of my own experiences at Charity Hospital, but I will give only one, a very rare and tragic episode. I was the junior interne who had given chloroform to the unfortunate woman. The scene was the chapel, one corner of which was used as an operating room. Alongside the operating table was another long table on which were placed some basins with water, 2 per cent carbolic acid solution, sponges and a collection of instruments. I cannot recall how the patient was cleansed, but I believe the abdomen was covered by a towel with carbolic acid solution.

The operator made a long rapid incision and inserted his hand into the opened abdomen. For some time he was puzzled by his findings and he discussed them with a friend and surgeon whom he had invited for the operation. This surgeon did not even wear a gown nor had he scrubbed his hands! All he did was to dip his fingers into the carbolic acid solution and explore the abdomen. One may fill in the details of the fate of the unfortunate woman!

There was but a short walk from the general hospital to the maternity pavilion where Garrigues would have enlightened those surgeons.

## THE CLINICAL DIAGNOSIS OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY<sup>1</sup>

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### TERMINOLOGY

Dilatation of the pulmonary artery is a frequent finding in many types of congenital heart disease, cyanotic as well as acyanotic. The most frequent cause is increased flow through the pulmonary artery as occurs in interatrial septal defect or patent ductus arteriosus. Rarely a disturbance in the rotation of the truncus arteriosus communis will result in a dilatation of the pulmonary artery, as for instance in the so-called Eisenmenger complex with or without interatrial septal defect. The supravulvular pulmonary artery dilatation in pulmonic or subpulmonic stenosis may also be explained hemodynamically, but this subject is still under discussion. In the case of idiopathic dilatation of the pulmonary artery, as the name implies, no primary hemodynamic disturbance is found to which this anomaly is secondary. It is believed to be a congenital anomaly, probably due to an unequal division of the truncus arteriosus communis. This definition should be strictly adhered to and the term be reserved for instances in which the following lesions are *not* found.

#### 1. Intracardiac shunts:

- (a) Interatrial septal defect without or with congenital mitral stenosis (Lutembacher's syndrome).
- (b) Interventricular septal defect (Maladie de Roger).
- (c) Eisenmenger's complex.
- (d) Eisenmenger's complex with interatrial septal defect.

#### 2. Extracardiac shunts:

- (a) Persistent patent ductus arteriosus.
- (b) Congenital arterio-venous aneurysm.

#### 3. Defects of the pulmonary valve or conus:

- (a) Stenosis of the pulmonary valve or pulmonary conus.
- (b) Bicuspid pulmonary valve; supernumerary pulmonary cusps; hypoplasia or anaplasia of one or more pulmonary cusps.

#### 4. Diseases of the lung:

- (a) Pulmonary fibrosis due to tuberculosis, bronchiectasis, etc.
- (b) Emphysema, bronchial asthma.

#### 5. Acquired or post-natal diseases of the pulmonary artery:

- (a) Of known etiology such as lues, rheumatic fever, "allergic" arteritis.
- (b) Of unknown etiology, so-called primary pulmonary arteriosclerosis.

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## DISCUSSION OF THE LITERATURE

The preceding discussion on terminology was intentionally presented before reviewing the literature, as it was deemed necessary to clarify the nomenclature which has not been strictly adhered to in previous papers. The first authentic case was briefly described by Wessler and Jachies (1) in 1923, and subsequently included in the report of a group of cases by one of the authors (2). The frequently quoted case of Zuber (3) of an almost varicose dilatation of the pulmonary arteries should properly be excluded, since in this five month old infant a patent ductus arteriosus was also found, although Zuber himself believed the persistent patency of the ductus was secondary to the increased pressure of the right side of the heart. Assmann (4) mentions as his first differential consideration the unequal division of the truncus arteriosus communis, but no case is reported in which this was the only congenital cardiac anomaly. Laubry (5) and Kourilsky (6) believe that the unequal subdivision of the truncus arteriosus is the important factor in instances of interatrial septal defect. For this reason only one of their numerous cases can be accepted as a genuine example of idiopathic dilatation of the pulmonary artery. This was a woman 82 years of age in whom the dilatation of the pulmonary artery was a coincidental finding; she had never exhibited any clinical signs or symptoms of the condition, and had died of a bronchopneumonia. The three cases published by Routier and Brumlik (7) in 1940 are not very convincing, as pulmonary artery dilatation is rather frequently encountered in chronic lung disease. Also in 1940, De Navasquez (8) and East (9) each published three cases of marked dilatation of the pulmonary artery, right atrial and ventricular enlargement, with advanced right heart failure. Neither the clinical history nor the post-mortem examination could adequately account for the lesion in any of these cases. Only slight arteriosclerosis of the pulmonary artery was found without any evidence of either lung disease, congenital or acquired heart disease. Both authors classified their cases as pulmonary hypertension of unknown origin. It is quite probable that these six cases represent instances of idiopathic dilatation of the pulmonary artery.

In none of the cases so far published has the diagnosis of idiopathic dilatation of the pulmonary artery been made with certainty during life, but only on post-mortem examination. With the introduction of the angiocardigraphic method and its development in the diagnosis of congenital cardiac disease, it has become possible to make the diagnosis of this condition during life, with a reasonable degree of certainty. Four new cases of primary dilatation of the pulmonary artery are herewith presented which have been studied by conventional roentgen and angiocardigraphic methods, and in which the diagnosis is acceptable, at least to the authors!

## CASE REPORTS

*Case 1. History.* L. C., a 37 year old white man, a policeman by occupation, had never been sick in his life, and even at the time of the examination was asymptomatic. In the

course of a periodic health examination an x-ray examination of his chest was done for the first time, and a marked enlargement of the pulmonary artery was noticed. He was sent to the Consultation Clinic of The Mount Sinai Hospital to have the nature of this abnormal shadow investigated.

*Examination.* The patient was a normally developed white man of average size and height. The radial pulses were equal, the blood pressure was 132 systolic and 88 diastolic; the circulation times and the venous pressure were normal. There were no abnormal pulsations visible on the chest wall. There was a short systolic murmur of low intensity heard over the apex and over the pulmonary area. The second pulmonic sound was accentuated. The electrocardiogram showed a regular sinus rhythm, no axis deviation nor

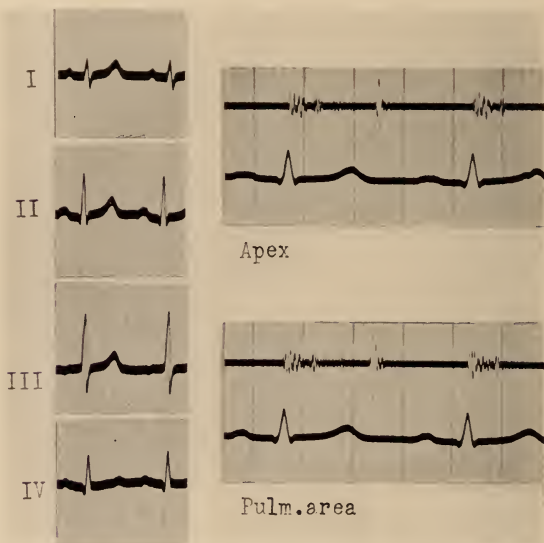


FIG 1. Case 1. The electrocardiogram is normal. Phonocardiograms reveal a systolic murmur of moderate amplitude over the apex and the pulmonic area. The second pulmonic sound is of slightly increased amplitude.

any other abnormality (fig. 1). The basal metabolic rate was minus 6 per cent. The Wassermann reaction was negative.

The conventional roentgenogram and fluoroscopy did not reveal any pathologic condition of the lungs. The heart was normal in size, shape and position. The main pulmonary artery was considerably enlarged, while the secondary branches appeared to be of normal caliber (fig. 2). The barium-filled esophagus showed no deviation. The pulsations of the pulmonary artery were not of the Corrigan type, nor was a hilar dance seen.

Angiocardiographic examination showed a markedly enlarged pulmonary artery, involving the main stem as well as left and right primary branches (figs. 3, 4 and 5). The



FIG. 2. Case 1. The conventional roentgenogram taken in the postero-anterior position demonstrates a considerable enlargement of the pulmonary artery and its main branches. The secondary branches appear to be of normal caliber. The size, shape and configuration of the heart are essentially normal.



FIG. 3. Case 1. Angiocardiogram taken in the postero-anterior position confirms the impression gained from the conventional roentgenogram.

secondary branches were perhaps slightly increased in caliber. There was no enlargement of any of the cardiac chambers. The sequence of visualization was normal. There was no evidence of a patent ductus arteriosus.



FIG. 4. Case 1. Angiocardiogram, left anterior oblique view, 2 seconds after onset of injection. The pulmonic artery and its main branches are considerably enlarged.



FIG. 5. Case 1. Angiocardiogram, left anterior oblique view, 6 seconds after onset of injection. The aorta is of normal size and outline. The sequence of the visualization of the cardiac chambers and vessels is normal.

*Case 2. History.* (Adm. 485122). L. H., a 20 year old woman was admitted to the hospital for a bilateral oophoritis two weeks after an attack of mumps. During a routine roentgen examination of the chest, a considerable enlargement of the pulmonary artery was found. The patient had always been and still was completely asymptomatic as far as her cardiovascular system was concerned.

*Examination.* The patient was a well developed white woman. The pulses were equal, the blood pressure was 110 systolic and 70 diastolic; the circulation times and venous pressure were normal. There were no precordial pulsations or thrills. There was a rather faint and short systolic murmur audible over the cardiac apex and one of slightly greater intensity over the pulmonic area. The first and second heart sounds were also reduplicated over both areas.

The conventional roentgen and fluoroscopic examination showed no pulmonary pathologic condition. The heart was normal in size and configuration. The main pulmonary artery was considerably enlarged and its pulsations were of normal amplitude. No deviations could be seen in the barium-filled esophagus.

Angiocardiographic examination showed a considerable enlargement of the pulmonary artery, particularly of the main stem, but also to some degree of the left and right chief branches. The secondary branches appeared to be of normal caliber. None of the cardiac chambers was enlarged. The sequence of visualization was normal and no evidence of a patent ductus arteriosus could be seen.

*Case 3. History.* (OPD 39-533). R. D., a 42 year old negress, had been treated in the Out-Patient Department of The Mount Sinai Hospital for minor ailments. In the course of a general examination she was found to have a systolic murmur, and on fluoroscopy an enlarged "pulmonary conus" was discovered. There was no history of lues, lung disease or asthma. The patient was asymptomatic.

*Examination.* The patient was a well developed slightly obese negress. The radial pulses were equal; the blood pressure was 124 systolic and 82 diastolic; and the circulation times and venous pressure were normal. There were no abnormal pulsations of the chest wall. Over and just below the pulmonic area a short systolic murmur could be heard. The second pulmonic sound was occasionally reduplicated and immediately followed by a loud sharply decrescendo high-pitched, musical murmur. Over the apex a systolic murmur of moderate intensity was heard, and in addition a distant very high-pitched decrescendo diastolic murmur (transmitted Graham-Steell (1)) was audible.

The electrocardiogram showed a regular sinus rhythm, no axis deviation and no abnormality.

The conventional roentgenogram and fluoroscopy revealed no abnormality of the lungs or heart. The main pulmonary artery was markedly enlarged, but the secondary branches much less so. The barium-filled esophagus showed no deviation. The pulsations of the pulmonary artery were prominent, but not of the insufficiency type (*pulsus celer et altus*, or Corrigan pulse). There was no hilar dance present.

Angiocardiographic examination revealed a marked enlargement of the main pulmonary artery and of its two primary branches, right and left. The secondary branches were slightly but definitely increased in caliber. No definite enlargement of any of the chambers was seen. The sequence of visualization was normal and there was no evidence of the presence of a patent ductus arteriosus.

*Case 4. History.* R. S., a 28 year old white physician was found to have a murmur over the pulmonic area and a marked enlargement of the pulmonary arterial area. The findings were interpreted by various authorities as being due to pulmonic stenosis or patent ductus arteriosus.

*Examination.* The patient was a well developed man. The radial pulses were equal, the blood pressure was 104 systolic and 68 diastolic, the circulation times and venous pressure were normal. There were no thrills or abnormal pulsations. There was a short systolic murmur of moderate intensity audible over the cardiac apex and pulmonic area.

Over the latter there was in addition a short, very faint early diastolic murmur (Graham-Steell murmur).

The electrocardiogram showed a regular sinus rhythm, no axis deviation nor any abnormality.

The conventional roentgenogram and fluoroscopy of the chest revealed no pathologic changes in the lung. The heart was normal in size, shape and configuration. The main pulmonary artery was considerably enlarged. The barium-filled esophagus showed no deviation. The pulsations of the pulmonary artery were of normal amplitude.

Angiocardiographic examination revealed a considerable enlargement of the pulmonary artery and of its two main branches. No enlargement of the cardiac chambers, no abnormal sequence of visualization and no evidence of patent ductus arteriosus could be detected.

#### COMMENT

The predominant clinical and laboratory findings of the four cases presented consist of the roentgenographic and angiocardiographic evidence of marked pulmonary arterial dilatation, in the absence of enlargement of any cardiac chambers, and any clinical or angiocardiographic evidence of the lesions enumerated in the introductory discussion. In two of the cases a Graham-Steell murmur was present; in all the cases a rather faint systolic murmur was heard over the apex and the pulmonic area.

A detailed discussion of the entire subject including the differential diagnosis will be reserved for a later publication; meanwhile one may say that with the introduction of angiocardiography (10, 11, 12) it is possible to make the diagnosis of idiopathic dilatation of the pulmonary artery by exclusion of other congenital lesions causing dilatation of the pulmonary artery, such as, for example, patent ductus arteriosus, interatrial septal defect and pulmonic stenosis.

#### SUMMARY

It is now possible with the aid of newer roentgenographic methods to make the clinical diagnosis of the rare condition, idiopathic dilatation of the pulmonary artery. The diagnostic considerations of four clinical cases are presented and illustrated.

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## FORTY YEARS' EXPERIENCE IN DISEASES OF THE DIGESTIVE SYSTEM

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It was my good fortune to make my first visit to Europe with my renowned uncle, Dr. Hiram N. Vineberg. During my frequent visits to his home, I often attended his clinics and was much impressed by his careful history and thorough examination of each patient. His operative technique was most skillful and meticulous. Under his guidance in Berlin, I followed his example in my post-graduate studies.

My first contact with Prof. Ewald was in his laboratory, where I found him making an examination of a stool specimen. He said that he did this himself in every case. In America this unpleasant procedure was reserved for a few selected patients. I resolved then and there to copy his example. When a patient objected to collecting a stool specimen, he was told that if the doctor was willing to examine it, he could at least send it in. This habit has saved me from making many grievous errors.

Ewald and Boas were then along in years, but Kuttner and Cohnheim were in their prime and very enthusiastic in their teaching. Forty years ago the change was taking place from the clinical type of practice to the academic, with stress being placed on laboratory methods.

Beaumont some years before had made extensive studies on the stomach and presented many brilliant observations on gastric secretion and digestion. Pavlov followed with his unique research and changed many of the accepted ideas and laid the foundation for much of our present knowledge of the physiology of digestion.

Kussmaul had brought the stomach tube into popular use and Leube and Riegel, with special test meals for secretion and motility, discovered many significant facts which threw much light on the interpretation of stomach disorders. It was through their research work that hyperchlorhydria and achylia were found to be the basis for some symptoms. The relief of pain with alkaline drugs was properly explained.

With all the clinical ability of these outstanding men there was still a great deal of guess work in diagnosis. Ulcer was usually not recognized until complications such as hemorrhage, obstruction or perforation occurred. Carcinoma often was not recognized until a mass could be felt or obstructive symptoms appeared. Various types of catarrh of the stomach were described and elaborate treatment offered.

Röntgen made his discovery in 1895 and soon thereafter Cannon used the X-ray to demonstrate that by means of an opaque meal, the digestive tract could be visualized. He was thus able to demonstrate many unique observations on motility and added greatly to our knowledge of the physiology of digestion. It was, however, some time before proper equipment was developed so that fluoros-

copy was made possible. Holz knecht was one of the first to recognize an ulcer on the fluoroscopic screen. Handek later described his characteristic ulcer niche.

A number of American workers, especially Pfahler, Cole, Stewart, Case and Carman, made important contributions to the use of the X-ray in gastroenterology. Graham and Cole found a method for visualizing the gall-bladder and this was of decided help in the differential diagnosis of right upper quadrant disease. All of these contributions added much to our knowledge of physiology and diagnosis and also were of great aid in accurately following the progress of disease.

During this time abdominal surgery made great strides and this led to still further progress in our understanding of pathologic changes and clarified many diagnostic problems. The surgeons taught us very much about the nature of many diseases and offered definite relief for ailments which formerly were treated for a long time without benefit.

When I began practice forty years ago, I firmly resolved that each patient should have the benefit of every laboratory aid. As soon as a new method was presented it was given a thorough trial and adopted if it had merit. A complete X-ray outfit was installed and also a basal metabolism machine as well as a cardiograph. Thus, whether the patient was poor or rich he was not given an opinion until all diagnostic procedures had been used. It is needless to say that such a complete systematic study of each case saved us from making many mistakes and was of decided benefit in planning the treatment. Many compliments we received were not due to being brilliant but rather came from thorough, careful study.

The gastroscope, largely due to Schindler's splendid efforts, has been a real aid in diagnosis and observing the progress of disease. We have found its main use as confirmatory to X-ray information. There are times however when it establishes a diagnosis when all other examinations have failed.

Investigators in the field of allergy and the vitamins have demonstrated a relationship to gastro-intestinal disease and these must always be considered in making a diagnosis and planning treatment. We must not be carried away by the enthusiastic reports in these special fields and should remember that proteins, carbohydrates, fats and minerals are still the most important constituents in our daily diet.

Lastly we must not forget, in accepting all the new ideas that laboratory research has brought to us, what the older clinicians have taught us. They had to use all their senses in making a diagnosis and then much wisdom in planning the treatment. They took the time to get well acquainted with the patient and his family. They studied his emotional reactions and his anxieties. The gastro-intestinal tract is intimately related to the nervous system and many of its diseases are influenced if not primarily caused by disorders of the brain and nervous system. When we have not succeeded in demonstrating an organic reason for the symptoms let us not forget that they may be on a psychosomatic basis.

The modern gastroenterologist in addition to a fine clinical background will have to be versed in pathology, biochemistry, radiology and neuropsychiatry. Psychosomatic medicine is rapidly taking a prominent place in modern medicine and, in the hands of scientifically trained clinical men, will be of great aid to suffering humanity.

## THE RECOGNITION OF INCIPIENT LIVER DISEASE

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Liver dysfunction occupies a prominent place in clinical medicine. The liver is one of the most important organs of the body. Only in recent years has its importance been recognized, and many students still enter their hospital training with little conception of its manifold functions. Teachers in medicine have for the most part failed to impress students with the aspect of early liver disease, giving them no systematic approach to the problem but impressing them with the myriads of tests which, for the most part, tell little of the early changes. The average student is taught cirrhosis from the standpoint of its complete picture, seeing it usually in its irreversible stage. Little emphasis is put on the prodromal manifestations, and due stress is not given to the incipient stage.

Long before the outstanding symptoms of cirrhosis are present, many criteria for diagnosis present themselves. The patient may early complain of fatigue, distaste for certain foods, headaches, vertigo, anorexia, nausea, flatulence, biliousness and constipation. There may be a gradual loss of weight and sudden attacks of weakness, particularly on even the least exertion. There are a sallow complexion, furred tongue and transitory dryness of the mouth. The muscle tone of the body is the first to suffer. Tasks which ordinarily are merely routine become slightly laborious. The patient notices his inability to focus his attention on the higher intellectual work. He becomes restless and even possibly depressed. His sleep is disturbed by turbulent dreams. He awakens from an apparently sound sleep with little or no energy. The skin becomes drier, and even various forms of dermatitis may become evident. So early is this picture that it frequently escapes the attention of the most astute clinician. The great reserve of the liver—the large factor of safety—makes the clinical picture all the more complicated.

Careful interrogation of the patient frequently reveals some etiologic factor. Alcohol may play an important role—not that one can prove that alcohol *per se* is the important factor, but the dietary balance is so definitely disturbed that dietary deficiencies develop sooner or later. It is now well known that any chronically deficient diet may lead eventually to liver disease. The American diet is reported deficient in the vitamin B complex. One might assume that the recent enthusiasm for concentrated vitamin preparations might have counteracted this. However, two factors have nullified to a large extent the possible beneficial effects of the increased vitamin intake: First, concentrated vitamin preparations are relatively expensive, and those who can afford to take them get an adequate amount in the diet anyway. Second, a large proportion of commercial preparations do not contain the whole vitamin B complex, are rich in thiamin

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and nicotinic acid but poor in other factors. There is some evidence to show this disproportion can do harm as well as good. Then, the desire for a "sylph-like" figure has undoubtedly induced lowering of the carbohydrate intake. Man has enough carbohydrate in sugars in reserve to last only about one-half day. The hyperlipemia brought about by deficient carbohydrate intake leads to deposition of fat in the liver, producing fatty cirrhosis. Therefore, not only is the glycogen reserve of the liver depleted, but the fatty replacement impairs normal liver function. Since an important function of the liver is detoxicating, toxic substances passing into it from the digestive tract may damage it further, owing to lowered local tissue resistance. These substances may even pass into the general circulation, in turn setting up tissue changes which interfere with normal metabolism and may even lead to retrogressive changes. The effects of various diets on liver damage have been recently investigated by Earle (1) and others, who found that feeding rats a diet containing ten per cent cystine leads rapidly to portal necrosis and hemorrhage and that prolonging such feeding produces cirrhosis of the liver. The type of diet definitely modified the mortality rate and the character of the lesion. Diets high in fat increased the severity of hepatic damage, while diets high in carbohydrate and protein and low in fat increased the number of mitotic figures, indicating regeneration. György (2) concluded that hepatic injury and fatty infiltration are definitely determined by dietary factors. He found that the addition of thiamin and riboflavin to the diet reduces the incidence of hepatic damage and that a diet low in casein and moderate to high in fat regularly induces hepatic injury after 100 to 150 days. The use of choline seemed to reduce the incidence of hepatic damage, and the addition of yeast was even more effective in preventing liver injury.

Besides faulty and injudicious diet, various other factors play a role. The frequent co-existence of gall-bladder and liver disease is well known. A chronically inflamed gall-bladder, particularly when associated with stones, leads to hepatitis. More evident is this if there are frequent episodes of acute suppurative cholecystitis. Even a quiescent gall-bladder filled with stones may lead to low grade or even marked changes in hepatic parenchyma. If there were no other justification for removing a gall-bladder with stones, this one complication would be sufficient.

Furthermore, our present industrial situation, with the inhalation of many chemical poisons, may lead to liver damage. Such diseases as syphilis and malaria are frequently etiologic factors. The tropical diseases to which our armed forces have recently been exposed will present a group of patients for future observation. These diseases will probably take their toll in the liver and lead to damage which may be only partially repaired. Even though the soldiers are young and have a great reserve at the outset, the rigors of war, the insult to their nervous systems and the inability to balance properly their diets for long periods might ultimately lead to persistent damage. Physicians will all have to be on guard for new types of liver disease never before recognized in such large numbers.

Unfortunately no one liver function test may satisfy all our needs. Certainly

the many so-called dye tests will not generally reveal liver damage in its early stage, even though one uses the more recent modifications with high concentrations. Those tests which demonstrate physiologic alterations and deviation from normal function will furnish the best leads. The principal difficulty with all these tests is that they should be done by well trained technicians and under well controlled conditions. The interpretation of their clinical significance nowhere nearly parallels in difficulty their technic. Of all the tests, those which seem to me at present to give the most help are the following (the reader is referred to any standard text for the methods and technics used):

1. The intravenous double glucose tolerance test is one of the most useful. In this test, the normal liver should produce a return of the patient's blood sugar level to normal at the end of one hour. Deviation from the normal range is indicative of liver damage. If damage is revealed after injection of 0.33 Gm. of glucose per kilogram of body weight, then the administration of 0.67 Gm. per kilogram should show a return to the normal level after one hour, if the liver is not too seriously damaged. In the latter case, one may have to use even 1 Gm. under the same conditions. Improvement in this function is significant of repair of the damaged liver after appropriate therapy.

2. The intravenous hippuric acid test offers an early index to dysfunction. It is important to recognize not only a deficient amount of excretion of benzoic acid in the urine, but also a higher than normal reading. The latter is significant of early liver disease and shows irritative phenomena, while lessened excretion reveals actual and definite damage. This test must be put in the hands of trained laboratory technicians.

3. The cholesterol-cholesterol ester ratio, if one uses the values of 65 to 70 per cent of the total cholesterol as the ester component, is of distinct value. Readings below 65 per cent show liver damage. The lower the percentage of esters, the more evident is liver damage. This test is valuable when properly done. Parenthetically it might be added that it is a useful one in evaluating surgical risk as far as liver reserve is concerned.

4. Tests for bilirubin metabolism are of great aid. The average clinician uses the icterus index more often. Various methods are used in different laboratories, and the normal range must be correctly interpreted, depending on the scale used. Higher than normal values may indicate liver damage without clinical evidence of jaundice, providing no extraneous factors interfere with the color of the serum. Quantitative estimation of serum bilirubin is used by some. The Van den Bergh or the Snapper method is most commonly used. Here again deviations from normal are indicative of hepatic damage. The routine qualitative Van den Bergh test is useful in differentiating the various forms of jaundice. Many other tests have been devised for serum bilirubin determination, and their usefulness depends on familiarity of the clinician with frequency of its use.

5. Under protein metabolism tests may be mentioned determinations of albumin-globulin ratio, the total serum protein and the colloidal gold reactions as well as cephalin-cholesterol flocculation tests. The last named is a very sensitive test, and after some training one can become efficient in its interpreta-

tion. It demonstrates liver disease long before gross clinical evidence is present. In our hospital laboratory it is routinely used by those studying liver disease. The colloidal gold reaction is difficult to standardize, and false reactions may present themselves unless definite standards are set up.

The plasma protein relations, e.g., the albumin-globulin ratio, have been particularly emphasized. Their importance cannot be over-estimated. Particularly are they significant of changes in the colloid-osmotic balance of the blood and tissue. Transitory edema may be explained on this basis.

All these tests may reveal liver damage, or one may be more indicative than others, depending on the degree of damage. The critical evaluation of their importance is directly proportional to the experience of the clinician in liver disease.

Other mechanisms may be involved, and laboratory data may have to be accumulated to explain various phenomena. The physician should familiarize himself with a few sound tests, and not be sidetracked by many test tube reactions which have no definite clinical significance.

Therefore, by studying the patient from the clinical and laboratory standpoint, one can arrive at an early diagnosis of liver disease, recognize it in its incipient stage, institute proper treatment, eradicate evident etiologic factors and finally substitute a life of well-being for one of possible invalidism.

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## CANCER OF THE CERVIX AS SEEN IN A HOSPITAL FOR FAR ADVANCED CASES

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This is an analytical review of the clinical manifestations, course and other pertinent data in 139 cases of cancer of the cervix which were admitted to Mercy Hall Tumor Clinic and Hospital, Detroit, from 1931 to 1943. All of these patients were in a far advanced stage. All but 25 died in the institution. By way of comparison, similar data from other studies of far advanced cervix cancer, chiefly Auster and Sala's (1) careful autopsy controlled series, and Behney's (2) autopsy report, are added.

Table 1 shows that 118 out of 139 cases (92 per cent) had had x-ray and radium treatment. Ten or 7 per cent had had no treatment. All of these were in the far advanced stage.

By way of contrast, Table 2 shows the treatment 262 cases received in Detroit in 1928 and 1930.\*

Though obtained from different sources, the data are comparable.

The changes in treatment which a decade has produced are: 1) Practical elimination of hysterectomy as a treatment for carcinoma of the cervix. In 1928-30, 11 per cent had pan-hysterectomy alone. Another 8 per cent had pan-hysterectomy plus irradiation. In this series only one case had hysterectomy. 2) More universal use of x-ray therapy. The earlier series showed that 56 per cent had had irradiation treatment (6 per cent x-ray alone, 54 per cent radium alone, 40 per cent both combined). In this present series 92 per cent had irradiation, and all but 8 per cent of these had both radium and x-ray therapy combined. There is now very little treatment with either x-ray alone or radium alone.

### AGE GROUPING

As shown in Table 3, 43 per cent were over 50 years of age. Comparing a few other series; Auster and Sala (1) give 47 per cent over 50, Behney (2) 46 per cent over 50, O. E. Todd (4) 44 per cent post-menopausal. This reiterates the well known fact that roughly 50 per cent occur before the age of the menopause is reached.

<sup>1</sup> From Mercy Hall Tumor Clinic and Hospital, Detroit, Mich.

Mrs. Margaret Wheeler, B.S., R.N., assisted in this work.

\* Reprinted from Saltzstein, H. C. and Topek, A. A., *Am. J. Cancer* 17: 951, 1933. These cases were collected through the Department of Health Cancer Division. All had died. The data on treatment was obtained at that time from the physicians and institutions that had cared for these patients.

TABLE 1

*Treatment received by 139 patients admitted to Mercy Hall in far advanced stage*

	CASES		PER CENT
X-ray alone.....	2		
Radium alone.....	8		
X-ray and Radium.....	118	128	92
Surgery (hysterectomy).....		1	1
No treatment.....		10	7
Total number of cases.....		139	

TABLE 2

*Methods of treatment 1928-30. Detroit Board of Health, Cancer Division\**

	1928	1930	TOTAL	PER CENT	MERCY HALL—43 TABLE 1— PER CENT
X-ray alone.....	9	0			
Radium alone.....	47	32			
Both.....	30	28			
Irradiation total.....	86	60	146	56	92
Radiation plus cautery.....	13	16			
“ “ amp. cervix.....	0	4			
“ “ laparotomy.....	2	0			
“ “ subtot. hyst.....	2	0			
“ “ panhyster.....	12 29	8 28	57	22	
Panhysterectomy alone.....	13	17	30	11	1
Cautery alone.....	4	2		5	
Amp. cervix alone.....	4	1			
Surg. diathermy.....	2		13		
No treatment.....	10	6	16	6	7
	148	114	262	100	100

TABLE 3

	MERCY HALL CASES	PER CENT	AUSTER	BEHNEY	TODD
			<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Age under 50.....	77	56			
Age over 50.....	58	43	47 (50-70)	46	44 (Post menopause)

## INITIAL SYMPTOMS

As shown in Table 4, 83 per cent started with hemorrhage, either alone, or with leucorrhea. Leucorrhea alone was the first symptom in 10 per cent. Pain and discomfort were the initial symptoms in 2.7 per cent. These are the usual figures of similar series; except that frequently pain alone represents 8-10 per cent of initial symptoms.

TABLE 4  
*Presenting symptoms at onset*

	MERCY HALL		SALTZSTEIN- TORCIK, 1928	1930	AUSTER
	CASES	PER CENT			
Hemorrhage	84	83	77	78	88
Hemorrhage with pain	21				
Leucorrhea with hemorrhage	2				
Spotting	9				
Leucorrhea	14	8	9.3	11.6	8
Leucorrhea with pain	4	7	9.3	8	7
Pain lower abdomen	1				
Pain bearing down	1				
Discomfort plus abdominal enlargement	2				

TABLE 5  
*Biopsy*

	CASES	
Squamous Cell.....	39	65
Adeno Ca.....	6	
Epidermoid.....	15	
Anaplastic.....	1	
Unknown.....	4	

## DELAY IN SEEKING ADVICE

As shown in Table 6, the number of cases (fifty-one) upon which these data were obtainable was not large since many were in a very far advanced stage on admission. Nevertheless 10 per cent still seek their first medical consultation after they have had symptoms more than one year.

O. E. Todd (4) had some interesting observations on this matter of delay in seeking advice and treatment, in a comparison of two series in 1933 and 1941. Whereas in 1933 he found a delay of six months between first symptoms and first examination and another six months before treatment was begun, eight years later there was the same delay of six months between first symptoms and first examination, but the physicians' delay between first examination and

treatment was now only one month. We could not get these last data, delay between first examination and treatment, accurately enough from our charts for tabulation.

TABLE 6

*Time after onset physician consulted. Data available in 51 cases*

	CASES	PER CENT	SALTZSTEIN- TOPCIK, 1928- 30-33	AUSTER
			<i>per cent</i>	
1 month.....	15	53	34	21% 3 mos.
2 months.....	4			
3 ".....	8			
4 ".....	4	16	26	21% 3-6 mos.
6 ".....	4			
7 ".....	3		27	
8 ".....	3			
10 ".....	2			
11 ".....	1			
After 12 months.....	1	10	13	25% appeared after 1 year
" 15 ".....	1			
" 18 ".....	2			
" 24 ".....	1			

TABLE 7

*Reasons given for terminal hospitalization. Data available in 93 cases*

	CASES	PER CENT
For pain.....	51	56
For bleeding.....	34	36
For weakness.....	26	28
Leucorrhea.....	5	5
Urinary increase or dysuria.....	5	5
With pain and bleeding.....	19	65
With lower abdominal pain.....	11	
With backache.....	18	
Vaginal pain.....	1	
Pain in leg.....	7	
Backache and leg pain.....	4	
With rectal pain.....	1	

#### REASONS FOR TERMINAL CARE

Table 7 lists reasons for terminal hospitalization. Thirty-six per cent sought admission because of bleeding; 5 per cent for leucorrhea; 65 per cent for pain; 28 per cent for weakness.

Thus, cervix cancer, in its far advanced stage, is a disease of pain, discomfort, weakness and hemorrhage. In the early stages, it is chiefly one of hemorrhage (60 per cent) and leucorrhea (10 per cent) (see Table 4).

## LENGTH OF TERMINAL HOSPITALIZATION

This varies with the economic status of the patient, and the presenting symptoms. Women from poorer families, single women, or those from homes in which there were no immediate relatives capable of caring for the patient, sought terminal hospitalization sooner, especially for severe pain or fistulae.

Table 8 shows: 52 (48 per cent) required hospitalization one month or less before death. These were chiefly cases of impending uremia. Forty-one or 40 per cent required 2 to 4 months. Fourteen or 12 per cent required from 4 to 13 months.

TABLE 8

*Data were available in 107 cases. Length of terminal hospital stay*

	CASES	PER CENT	AUSTER
2 weeks or less.....	25	48	33% less than 1 mo.
2-3 weeks.....	27		
2 months.....	17	40	23 of 124 (20%) 1-2 years
3 ".....	13		
4 ".....	11		
5 ".....	4	12	
6 ".....	2		
7 ".....	3		
8 ".....	2		
9 ".....	2		
13 ".....	1		

## TERMINAL SYMPTOMS—PROGNOSIS

In Table 9 an attempt has been made to determine how long patients with particular symptoms are apt to require care or hospitalization. This is an important question often asked by the family, and it is hoped that others who have access to many of these cases, will continue such inquiries. To our knowledge not much has been written about this particular phase of far advanced malignancy.

It is apparent that two-thirds of the cases with back pain must be cared for for more than six months before the Good Lord ends all. Leg pain, groin, vaginal, anal pain, similarly are indications that the patient will probably linger for more than six months.

Pain in the back is the outstanding symptom of far advanced cervix cancer. It is usually in the low lumbar and sacral region, often unilateral, frequently radiates down the back of one thigh (rarely both), occasionally down the posterior calf to the heel, often radiates around to the inguinal region, groin or perineum. In none of these cases was it described as going above the umbilicus.

It begins as an ordinary low back ache, relieved by rest in bed, warmth and general body care or a bit of codeine and aspirin. Within 1 to 2 months it

becomes severe, continuous, varying in intensity, often vice-like, and intractable. It usually makes the patient bedfast for 3, 4 to 6 months before exitus, and, except for the pain caused by spinal metastases from breast cancer, is perhaps the most severe form of suffering commonly encountered in terminal malignancy.

Although it has been ascribed to pressure on the lumbar and sacral nerves, involvement of the sympathetics in the pelvis, and irritation of the nerve ends exposed in the open ulcerated areas, Schmitz (5) and many other urologists describe it as the syndrome of chronic ureteral obstruction. The ureteral complications of carcinoma of the cervix have excited considerable interest during the past few years. At the time of death 50 to 75 per cent have ureteral strictures, with ensuing hydro- and pyo-nephritis. There may be involvement when the patient is first seen, hence most of these women should have intravenous urography before treatment, at least if the disease is advanced.

TABLE 9

*Prognostic value of symptoms. Duration of life from onset of pain to exitus*

	CASES	1 MO. OR LESS	1-6 MOS.	7-12 MOS.	1-2 YRS.	2-3+ YRS.
Pain in back.....	17	3	1	5	6	2
Pain in leg.....	4	1	1	1		1
Pain in abdomen, right or left lower quadrant, groin.....	8	2	1	3	1	1
Pain in vagina, rectum.....	2		1		1	
	31	6	4	9	8	4
		10 cases		21 cases		

There has been some controversy in the literature regarding whether the stricture is caused by post-radiation fibrosis (and if so, how frequent is this the case) or whether cancer is invariably present in the pelvis when stricture is noted. If the latter is true no hope for cure can be promised once this complication is established.

If the stricture is due merely to edema following radiation, it should be amenable to dilatation in many cases.

Jaffe (7) described two cases in which ureteral dilatation relieved backache, and the patients were well five years later. Valk (11) relieved 15 per cent by means of ureteral dilatation.

Ureteral dilatation does relieve this pain. We have seen severe backache disappear as soon as 20 cc. was drained from a distended pelvis. However, there is universal apprehension about leaving catheters *in situ* more than 48 hours, and although pain may be relieved for 2 to 3 days to 2 weeks or more, it usually comes back.

The more recent opinion is that cancer has practically always extended to the broad ligament, either as a dense hard mass in the pelvis or invading the peri-

ureteral tissues, by the time a stricture of the ureter is present. This is the reason that ureteral dilatation is effective in only a small number of cases.

Cutaneous ureterostomies have been done more frequently during the past 5 to 10 years. Valk (11) does bilateral cutaneous ureterostomies as soon as hydroureter is noted on both sides. On the other hand Auster and Sala (1) do not think any palliative surgery is indicated, as it "adds a further problem and does not add to the patient's comfort or length of life."

If the operation is done to postpone threatened uremia, that is of doubtful benefit. If it is to relieve intractable backache, which according to Table 9 may last more than six months, the urinary drainage onto the skin may make for a more comfortable patient. As yet, we have not had much personal experience with this operation.

TABLE 10

*Fistulae*

	MERCY HALL CASES	SEAMAN	AUSTER AND SALA
Recto-vaginal.....	25	12	
Vesico-vaginal.....	6	8	
Recto-vesico-vaginal.....	2 33	20 in 149 cases = 13.4%	37 in 124 cases = 30%
Treatment received			
Radium alone .....	1		*
X-ray and Radium.....	32		
Untreated.....	0		7

\* Thought to be more frequent after high intravaginal radium dosage.

## FISTULAS

In our series by far the most common are recto-vaginal. These follow either a disintegration of the posterior vaginal wall which has become invaded by cancer, or a dense stony mass in the cul de sac which by pressure against the anterior rectal wall has softened and ulcerated into the rectum.

The abdominal anus of a colostomy is much easier to take care of and more comfortable than an incontinent recto-vaginal fistula.

Further experience with suction such as is used for decompression of the upper alimentary canal (12), applied to the vagina through a gauze wick has been satisfactory. The gauze becomes encrusted with urinary salts and should be renewed every six to eight hours; otherwise there is the usual offensive odor of decomposing urine. No irritation of the vagina has followed even after application of this suction for several weeks, and the bed sheets have remained dry.

## CAUSE OF DEATH

Table 11 is from clinical observation only, and hence is presented as a basis for discussion rather than scientific accuracy.

We list hemorrhage as the cause of death in 16 per cent (15 cases) of our cases.

In three the hemorrhage was a sudden profuse flooding probably from rupture of the lower segment of the uterine artery. In five cases there was repeated hemorrhage over a period of two to three weeks. Seven cases had no data regarding duration of bleeding.

TABLE 11  
*Clinical cause of exitus*

	CASES	PER CENT
Treated Cases:	138	
Uremia.....	39	28
Hemorrhage.....	23	16
Anemia.....	10	7
Cachexia.....	3	2
Pneumonia, lobar.....	1	7
Pneumonia, bronchial.....	3	2
Intestinal obstruction.....	1	7
Cardiac failure.....	1	7
Pulmonary tuberculosis.....	1	7
Sepsis.....	2	1.4
Hyperplexia.....	1	7
Unknown.....	44	32
Untreated Cases:	10	
Uremia.....	3	
Unknown.....	4	
Cerebral hemorrhage.....	1	
Anemia.....	1	
No information on three.....		

In Behney's series hemorrhage caused 10 per cent of deaths. In Auster and Sala's cases, hemorrhage was the primary cause of death in 13 per cent (clinical diagnosis) and 8 per cent autopsy diagnosis, while as an associated cause of death it was an additional 9.6 per cent and 7.3 per cent respectively.

In a certain number of cases, a pelvic abscess ruptures into the abdominal cavity. Behney mentions this as having occurred in two cases, one of them due to reactivation of pelvic inflammation by radium. In Auster and Sala's cases, although it was not recognized clinically at all, pathologically it was the primary cause of death in 15 per cent. It is therefore silent, unsuspected, and more frequent than one might think.

Cardiac failure and pneumonia are often terminal manifestations. The pneumonia may be a terminal manifestation of sepsis.

However, in any series of deaths from cancer, a few must die from causes other than cancer—cardiac failure, cerebral accidents, etc. In our series, one died of pulmonary tuberculosis, one of heart failure not associated with cancer. Behney had 4 per cent (7 cases) in whom the cause of death was not cancer, *i.e.*, 4 heart disease, 2 cerebral hemorrhage, one pancreatitis.

Another group which is becoming of interest since patients live longer is distant metastases. Behney noted 44 per cent distant metastases in untreated, 21 per cent in treated patients; the distribution was the same in both groups. In 13 cases there was bone involvement. In 40 per cent there was extension beyond the abdomen. Auster and Sala record 27 per cent in which metastases occurred beyond the pelvis. In eight cases there was extensive skeletal involvement.

These distant metastases may be impossible to recognize clinically but one must appreciate that they do occur. We have seen one patient with carcinoma of the cervix who developed twelfth lumbar spinal metastases, then left supraclavicular nodes, then terminal jaundice (not included in this series). Seaman (10) mentions 3 metastases to the spine in 149 cases.

We have seen 3 to 4 cases where there was enormous edema of one leg, due to an extensive intrapelvic mass pressing on the return flow from the leg, and in one case gangrene of the foot developed. Behney mentions this as due to infected thrombophlebitis.

The chief interest in the cause of death, however, is the large group of urinary sepsis cases. As mentioned, all recent observers place this as 50 to 75 per cent of the total causes of death. Auster and Sala list uremia as the primary cause of death in only 4.8 per cent, but associated damage to the urinary tract (hydro, pyonephrosis) is present in 72 per cent of all cases.

The uremia starts insidiously. First there may be a little unexplained nausea, which persists. After 1 or 2 weeks, there is vomiting, and this becomes more frequent. Then mild drowsiness, perhaps headache, follow, and it is noticed that less narcotic medication is necessary (1 to 2 weeks more). Next the patient sleeps 2 to 3 hours during the day in addition to all night. Then comes stupor, extreme nausea and vomiting, urinary odor to breath, and a final 1 to 2 weeks of coma and anuria. The whole clinical termination usually takes 4 to 6 weeks; it is not a rapid death. There frequently is infection; then fever is added. There is also anemia with a pasty color out of proportion to the amount of ascertainable carcinoma. It is probably the anemia of advanced nephropathy.

Blood urea nitrogen, as noted by several observers, is not elevated until the final stage.

#### DURATION OF LIFE

Table 12 contrasts the duration of life of treated and untreated cases. No untreated cases lasted more than 3 years, whereas 15 treated cases did, 10 of them more than five years.

Thus treatment definitely prolonged the lives of many of those who ulti-

mately died. Nevertheless the number of treated cases whose entire duration of illness from onset to death was one year or less (51 out of 127) is discouraging.

It is well known that the average duration of untreated cervix cancer is short, usually it is given as 16 to 17 months, or perhaps 15 to 20 months (13). However, the duration varies widely in occasional instances. Cases in which the entire life history of the disease was five weeks, nine weeks, four months have been reported. On the other hand 16 per cent of Williams' untreated cases

TABLE 12

*Duration of life from onset to death. Data available in 127 cases*

	CASES TREATED	CASES UNTREATED
5 years and over.....	10	
4 " " ".....	4	
3½ " " ".....	1	
3 " " ".....	5	
2½ " " ".....	6	
2 " " ".....	20	
1½ " " ".....	12	
1 " " ".....	34	
½ " " ".....	14	
Under ½ year.....	3	
Unknown.....	18	
	—	
3 years.....		1
2 ".....		1
1½ ".....		1
1 ".....		2
Less 1 year.....		1
Unknown.....		4

Total duration of disease is short.

Average length of life is 16.7 mos.

lasted three years One case lasted eleven years (Borker); one twenty-two years, (Martin) with a fungating growth in the vault of the vagina all this time (13).

#### SUMMARY

In a review of 139 cases of carcinoma of the cervix observed in an institution for far advanced cases:

1. X-ray and radium in combination is now the only treatment these far advanced patients receive.

2. Fifty per cent occur before menopause.

3. Initial symptoms of cervix carcinoma are hemorrhage and leucorrhea.

4. Ten per cent sought advice one year after symptoms started.

5. Symptoms of the far advanced stage are pain and weakness more preponderantly than bleeding and leucorrhea.

6. A large percentage of these patients require bedfast hospital care for several months.

7. Back and leg pains are present for six months or more before death (small series of observation). Ureteral strictures, present in 50 to 75 per cent of these cases at time of death have been relieved by cutaneous ureterostomies. Opinion as to the status of this procedure is divided at the present time.

8. Recto-vaginal and vesico-vaginal fistulae are frequent.

9. Cause of death is frequently uremia, with sepsis often added. General metastases are more frequent since many patients now live longer following treatment. Terminal uremia starts insidiously.

10. There is evidence that irradiation treatment prolonged life in this small series of patients all of whom died.

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# CONSTITUTIONAL INADEQUACY IN WOMEN

## THE GYNECOLOGICAL ASPECT

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It is a truism that except for infectious diseases, most of the ills which distress women have their origin in the reproductive tract. From the delayed or precocious menstruation at one end of the female cycle, through functional bleedings premenstrual tensions, dysmenorrhea followed by the traumatism of childbirth to the neuroses phenomena of the menopause, women struggle with more or less illness. When one adds to the list the neoplasms not to mention endocrine disturbance, the array becomes formidable indeed.

It is another truism to state that women react in widely different ways to their reproductive activities. Some fortunate ones never have any abnormality and go through life vigorous in girlhood, serene in matronhood and stately in old age.

Others react so profoundly and suffer such tremendous psychic disturbances under the strain of being a woman that they either break completely or are found as more or less constant inhabitants of gynecologic offices. It is this latter group that warrants a survey of the position of gynecologists with regard to them.

Alvarez (1) recently published a most thoughtful and timely paper upon the subject of "Constitutional Inadequacy" in which he calls attention to the many persons of both sexes who are "constitutionally inadequate persons unable to stand up well to the strains of life. They cannot be cured as they hope to be, by the discovery and eradication of any one local disease." Every gynecologist of experience has usually under his care a group of women who are invalids under the old popular use of the term.

These are the women who suffer from unexplained dysmenorrhea, from irregularity of the flow, who have severe premenstrual tensions often with intense migraine and who frequently display marked asthenia and depression during ovulation, even if they escape the common *mittel schmerz*. They do not stand pregnancy well and are victims of uterine inertia when in labor.

Lack of bodily vigor, inability to sustain effort whether mental or physical and many other pains and disabilities complete the picture. Some of these evidences of disease may be properly ascribed to endocrine imbalances and some relief is occasionally obtained by the careful use of hormonal preparations. However, in general, even the most intelligent endocrine treatment is unsatisfactory and new trains of complaints arise to replace those which have been relieved.

Naturally these unfortunates seek much and varied medical advice for the alleviation of their protean ailments and because so many deviations from the norm are present the treatments suggested and applied are as numerous as the patient's complaints. The more careful and detailed the physical examination of such women the more local lesions are uncovered and treated with high

hopes on the part of both physician and patient that now at last has been disclosed the underlying cause of the disability and that by its removal a cure will result. High hopes usually doomed to complete frustration after the passage of a few weeks.

These are the women who emerge from the office of the oculist equipped with glasses, from the otolaryngologist minus their tonsils, the gastroenterologist equips them with a ptosis belt and their gall bladders have been periodically drained or removed. The appendix, of course, has long since been ablated and during the course of all these procedures a steady obligato of varied and multiple hormone injections has been the sustaining note of treatment.

When we come to the gynecologic management of such patients the cup of therapeusis runneth over indeed. The stenosed cervix has been dilated, the retroverted uterus appropriately suspended, the ovary, victim of multiple follicular cysts has been resected and the hydrosalpinx excised; all this to the same undertone of endocrine injections. The above statements are not made in a vein of captious criticism nor are they to be construed as ironical or possessed of a somewhat false sense of humor. The various procedures outlined and many, many others have been carried out by competent and serious medical men to whom the patient has appealed and who, after the most meticulous study and consideration of the case, have felt honestly that the eradication of a discovered variation from the normal in one or another organ will lead to a general improvement.

Furthermore, when a woman presents herself to a gynecologist with a demonstrable lesion in the reproductive tract, it is difficult to say that proper management of that lesion will not lead to cure. The important fact seems to lie in the recognition of constitutional inadequacy and here Alvarez has so ably summed up the matter that I venture to repeat his conclusions:

"When the patient walks into the office the diagnosis will be apparent. There, perhaps, will be a frail looking or scrawny woman, whose tissues were evidently made up out of poor materials. Perhaps the hand of the potter slipped a bit so that the body is poorly proportioned and poorly put together. Perhaps it looks as if, during the early years of development, the pituitary gland and the ovaries, which preside over sexual development, failed to do their job properly.

"The curse of inadequacy will become even more apparent as soon as the long story is told of many illnesses, many diagnoses, much fatigue, much disability and much strenuous but futile treatment. Surely the minute the physician gets this history he should realize that he isn't going to make the patient over into a 'husky', no matter how many localized diseases he succeeds in finding and removing.

"Another way of recognizing the inadequate woman is to watch her as she goes through her tests; a little pain, a little diarrhea, a sleepless night, or some bad news from home, and she will be prostrated and confined to bed for a day or two.

"As I have already said, the physical examination may or may not strengthen the impression that the patient is constitutionally inadequate. In a woman

the uterus may be found to be infantile in type, the breasts may be poorly developed and nodular, the body hair may have a masculine distribution, the thoracic cage may be unusually long, with a narrow epigastric angle, and the pelvis may be flat and simian in type, but then again none of these physical peculiarities may be present."

It is a common practise to apply the term neurosis or psychoneurosis to designate this general condition but these words seem faulty because the difficulty lies in a general bodily deficiency rather than a process originating and limited to the central nervous system.

It is probable that these people are deficient in those many factors of safety inherent in healthy human beings in whom all organs or systems are constructed to withstand the extra load of transitory infection, traumatism, emotional disturbances and so on. For these reasons the designation of constitutional inadequacy as proposed by Alvarez seems as nearly descriptive as may be.

The management of this condition is naturally most unsatisfactory. When an ill and depressed woman consults her physician it bespeaks a lamentable weakness in the profession to tell her simply that she was born below par and must forever remain so. The most careful and detailed study is necessary to determine whether one's impression of inadequacy is correct or whether there may exist some pathologic process which may explain the complaints.

The essential thing to be remembered is that a mere pathologic finding which does not reasonably account for the illness should not be regarded as causative and treated by surgery unless the indication is definite and apparent.

It has been said at the outset that constitutionally inadequate women locate most of their primary difficulties in the reproductive organs, specifically the functional ovarian-endocrine cycle and consequently the gynecologist is the specialist upon whom a great part of the management of such patients evolves.

Here, a long period of observation of these women has led me to offer a proposition which is stated with much diffidence, because it may be misinterpreted so easily.

The thesis is as follows: given a woman who has been determined to belong in the group of constitutionally inadequate persons and who has sufficient abnormalities of the pelvic organs to warrant operative interference; total ablation of the internal organs of reproduction regardless of the age of the patient and followed by appropriate endocrine and hygienic management of the ensuing menopause, offers a greater hope of improvement of the patient's health than any other procedure.

The foregoing statement is not to be taken as advocating indiscriminate castration of women upon wide indications. Far from this, the writer is extremely loath to operate upon inadequate women at all and the point must again be stressed that total ablation is only to be done when sufficiently severe lesions of the internal genitalia exist to warrant some form of pelvic operation.

This plan of treatment is by no means new. In 1876 Robert Battey (2) of Rome, Georgia, read a paper entitled "Extirpation of the Functionally Active Ovaries for the Remedy of Otherwise Incurable Diseases" at the first meeting

of the American Gynecological Society. This paper and others which followed made the so-called "Battey operation" at first notable and then notorious. Older gynecologists will remember the obloquy heaped upon the procedure and its proponents as the almost criminal unsexing of young women.

Like many another enthusiast, Battey rode his hobby too strongly and his followers further expanded the original indications until strong measures of rebuke were forced upon the more conservative element of the profession in order to check what had grown to be a vicious practise.

One reason for the severe condemnation which this operation received was due to an unfortunate choice of words by its proposer who termed it "Normal Ovariectomy". In the paper above alluded to Battey explains this term by stating that by definition a thing is normal when strictly conformed to those principles of its constitution which mark its species. "When I extirpate an ovary," says Battey, "which, although it may be diseased, is easily and distinctly recognizable as an ovary, I feel that I am doing the operation of ovariectomy normally." It is easy to understand how such a strained use of words led to great misunderstanding of the author's true position.

Battey's defense of the indications for his operation are strongly expressed and in most idealistic fashion. "So great is the sanctity attached to the functions of the ovary and the testicle, in the professional as well as the popular mind, I hold that neither of these organs ought to be sacrificed to the surgeon's knife excepting for just cause and provocation, and after mature deliberation. I go further than this, I believe that these organs should alone be sacrificed for grave causes, and then only as a dernier resort, when the hitherto recognized resources of our art have been expended in vain. No part of the human body ought to be invested with such dignity and value that it may not properly be sacrificed, if need be, for the welfare of the whole.

"In my opinion the removal of the functionally active ovaries is indicated in the case of any grave disease which is either dangerous to life or destructive of health and happiness which is incurable by other and less radical means and which we may reasonably expect to remove by the arrest of ovulation or change of life. I do not propose it for any case which is curable by other means."

Surely this is a rather admirable statement of a surgeon's position as concerns a mutilating operation and it should be noted that the discussion which followed the original presentation was in the main commendatory. Skene, Parvin, Peaslee Noeggerath and Goodell; the leaders of our specialty in that day were enthusiastic in their praise although differing in various details from the essayist.

However in the course of a few years the procedure of ovariectomy had become a widespread evil, performed upon the flimsiest indication and, as was natural in the state of abdominal surgery seventy-five years ago, carrying a high mortality.

The period of reaction which followed brought with it the era of absurd conservatism in which it was deemed improper to sacrifice any but obviously diseased tissue. This was the time of resection of cystic areas in ovaries, or uni-

lateral salpingectomy and the like. Two notable Philadelphia gynecologists, Baldy and Price, raised their voices in vain against this overemphasized conservatism but were among the small minority who recognized the futility of these procedures.

Of late years the pendulum has swung back toward the midline and intelligent and conservative radicalism is coming into its own. When one studies the detailed histories of Dr. Battey's earlier patients, it becomes apparent that he was treating typical cases of constitutional inadequacy although this term had not yet been developed. Later the indications were expanded to a highly improper degree.

In summary it may be said that constitutional inadequacy as defined by Alvarez is a very definite state which is not often amenable to complete cure by any therapeutic measures whatsoever and that these unfortunates pass their entire lives in a greater or less degree of invalidism despite the best efforts of medicine.

In women belonging to this category surgery is in general inadvisable even though distinct abnormalities are discovered, unless the lesion is such that it may reasonably be thought to be the etiologic factor producing the disability.

The diagnosis of constitutional inadequacy is not difficult but great care must be exercised lest patients be put into this group too hastily and before detailed study has demonstrated the presence or absence of some definite and causative pathologic process. In many women ill health centers about the ovarian functional cycle and it is a notable fact that many of them tend to improve spontaneously after the menopause. All of us know well the women who have been below par all during their reproductive life but who blossom out after the climacteric to become active and vigorous matrons, with only a residue of neurosis remaining from their previous state of general ill health.

It has been stated that surgery is to be avoided whenever possible in these patients, but when pelvic operation is definitely indicated the patient is best served by a salpingo-oophoro-hysterectomy than by any lesser measures.

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## THE PRESENT STATUS IN THE TREATMENT OF CERVIX CANCER

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As Hiram Vineberg pointed out at a meeting of the American Gynecological Society in 1919, cancer of the cervix is relatively infrequent in Jewish women, yet this disease is so widespread throughout the world that it demands the special consideration of all gynecologists.

The past fifty years has shown many interesting developments in the treatment of malignancies of the cervix. In the last decade of the nineteenth century we witnessed the development of a surgical technique that proved in a much greater number of cases than heretofore, to effect a cure of this condition. This consisted of the radical removal of the uterus, adnexa and upper vagina together with its surrounding connective tissue. Schauta devised an operation to remove these structures *per vaginam*, whereas Wertheim's panhysterectomy was done by laparotomy and usually included some of the tributary lymph glands. Both operators lived in Vienna and soon had a following throughout Europe and other countries. In the United States, John Clark and Brettauer were strong advocates of the abdominal procedure. Today there are still some like Frank Lynch in San Francisco and Victor Bonney in London who have a large successful experience with this operation. In general the vaginal excision never gained the popularity of the abdominal operation. Even in the hands of the specially trained gynecologist these operations, however, had an alarming mortality and morbidity, unless limited to the small group of early cancers of the cervix. The operative death rate ranged from 6 per cent to 15 per cent. In the hands of the inexperienced surgeon this percentage was doubled.

It was not surprising therefore that when in the decade from 1910 to 1920, it became evident that radium and deep x-ray therapy would produce regression of cervix cancer, there was a strong movement to put surgery in the discard and rely on radiation as a therapeutic measure in this disease. Not only was it found that the primary mortality was thereby greatly reduced but a large group of patients with conditions too advanced for surgery, could still be alleviated and at times cured by these agents.

In the following decade the astounding results produced by radium and x-ray in the treatment of cervix cancer led to such a widespread use of these agents by untrained persons that serious damage and deaths resulted in many instances. Doctors who would hesitate to do a major operation, did not refrain from using these radiation measures without any preliminary experience. In fact even at the present time there is still much malpractice in this form of therapy. The result was an ever increasing number of severe painful burns of the pelvic organs, with bladder and rectal fistulas a common sequel of the treatment.

Even with the greatest precautions and experience serious complications are at times attendant upon radiation treatment. In recent literature we have

numerous reports of such occurrences. Duvergey reports fifteen cases of radionecrosis of the bladder following radium. Often an interval of many years elapses between the treatment and the necrosis and the cure of these complications is a slow and painful process. Aldridge describes serious intestinal injuries following x-ray therapy. Of 142 patients treated for carcinoma of the cervix uteri, 31 developed post-irradiation intestinal injuries including 23 intestinal strictures. In eleven patients the lesions were so serious as to require surgical intervention, usually in the form of a partial resection or a colostomy. In the discussion following Aldridge's paper, J. V. Meigs stated that of 34 patients with stricture and obstruction out of a total of 800 radiated cervical cancers, 22 were operated on by colostomy or intestinal resection. In about half of these patients an interval of over one year had elapsed between the high voltage therapy and the intestinal obstruction. In a relatively high percentage the million-volt machine was employed.

The immediate risks of radium treatment have also been found to be considerable. In many instances the presence of a pyometra or tubal infection has been responsible for an acute, at times fatal, peritonitis. Owing to difficulties in locating the uterine canal and the friability of the cancer-infiltrated tissues, perforation of the uterus with resulting mortality is not a rare occurrence. For these reasons we find the immediate post-radiation death rate given as between 2 and 3 per cent.

According to Cutler the risks attendant on the radium treatment of the advanced cases of cervix carcinoma are far greater than in Group II cases. Hemolytic streptococci are frequently present and greatly increase the dangers of treatment. Of 22 carriers of virulent streptococci, 5 or 18 per cent died, 8 showed severe complications and 13 showed a smooth convalescence. Treatment with sulphanilamide has helped to improve results but the danger of a fatal outcome is still very considerable.

If I have stressed these complications of radiation treatment, it is primarily to show that it too, as well as surgery, has its inherent dangers. I am convinced that the pendulum has for too long a time swung away from surgery in the treatment of cervix cancer. The results of those trained in the technique of cancer surgery is such that in the group of early cases they have not been surpassed by any advocates of radiation treatment. In Group I cases that are good operative risks, the primary operative mortality should not exceed 5 per cent and the five-year and ten-year survivals run between 50 and 60 per cent. I have for some time been struck by the comparative rarity of recurrences between five and ten years where a hysterectomy has been done as compared with similar cases treated by radiation only.

In Group II cases of cancer of the cervix I have since 1930 adopted the policy of treating the primary lesion in the cervix and upper vagina by radiation and following this have surgically removed the important pelvic lymph nodes (hypogastric, obturator, ureteral, external iliac) from both sides. This operation of iliac lymphadenectomy, when carried out in cases presenting no surgical contraindications (heart or kidney disease, diabetes, obesity), has in 182 such cases,

done mostly at Barnard Free Skin and Cancer Hospital, shown only three post-operative deaths (1.6 per cent). The operation is therefore not dangerous and since the five-year survivals in a series of 70 cases were 38 per cent as compared with a similar series of cases treated by radiation only in which the five-year salvage was 23 per cent, the advantage of removing the lymph nodes is definitely proven. One patient operated in October 1930 with a large cancerous hypogastric lymph node, is still free of any evidence of cancer.

In the large number of Group III and IV cervix cancers, we can of course employ only radiation methods of treatment, but here we can hope to save only a relatively small number of cases.

In the large collective abstract concerning radiation treatment published by J. Heyman through the League of Nations Health Organization in 1939 the results are published from several cancer clinics and hospitals in Europe and America with the following five-year survivals in the four principal groups. Unfortunately some of the hospitals, as shown by their own statements, do not strictly follow the League of Nations classification as laid down by Heyman. Cases are included in Group III that should have been in Group II, so that the survival rate in Group II is probably less than the figures given in this composite tabulation:

	NUMBER OF PATIENTS TREATED	ALIVE WITHOUT RECURRENCE	RELATIVE CURE RATE (PER CENT)
Group I .....	871	498	57.2
Group II .....	2,305	867	37.6
Group III .....	3,420	754	22.0
Group IV .....	1,360	75	5.5
Unclassified .....	2	0	0
Total ..	7,958	2,194	27.6

In many recurrences after surgery or radiation therapy, additional radiation can be given with benefit in many cases. Scheffey reported 269 such cases with 36 survivors for five years or more.

Regarding the results of surgical treatment by radical panhysterectomy of cervical cancer, Frank Lynch collected 3239 Wertheim operations from fifteen different clinics. A tabulation of the results showed that 40.5 per cent survived a five-year period but 16.5 per cent died as a result of the operation. Many of these operations were done in Group II cancers. This accounts for the high primary mortality and relatively low cure rate. Where only Group I cancers were included the mortality in Lynch's experience ranged between 6 to 8 per cent and the five-year cure rate was over 60 per cent. I reported in 1935 a total of 43 Group I cases operated by Wertheim's method from 1912 to 1930 with two postoperative deaths (4.6 per cent) and 26 five-year survivals (60 per cent). Lynch emphasizes the great advantage of surgery over radiation in eliminating the recurrences between five and ten years after treatment. After radiation in

the Group I cases there was an additional drop in salvage of 10 per cent in this second five-year period, whereas after surgery, the drop was only 2.8 per cent.

#### SUMMARY

1. While the *immediate* mortality following radiation treatment is considerably less than that following hysterectomy, the *late complications* often leading to *death* are definitely more frequent. The damage done by surgery is immediately evident, whereas the injuries produced by radiation may take years for development.

2. In Group I cancers (League of Nations classification) surgery in patients who are good operative risks presents definite advantages over radiation.

3. In Group II cancers radical surgery gives too high a primary mortality, hence radiation of the primary tumor is advisable. This can with advantage be combined with surgical removal of tributary pelvic lymph nodes, since the primary mortality of this procedure is only 1.6 per cent and the five-year additional salvage by this operation is 15 per cent.

4. In Group III and Group IV cancers radiation should alone be considered even though it may often be attended by fatal complications and can be expected to save only about one out of every five or six patients.

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# THE TREATMENT OF URINARY FISTULAE<sup>1</sup>

## AN ANALYSIS OF PERSONAL CASES

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Urinary fistulae have existed from immemorial time. The earliest recorded case was that of an Egyptian Queen, who reigned about 2050 B.C., and whose mummy showed the presence of a large vesico-vaginal fistula and a contracted pelvis. The condition was considered incurable until early in the nineteenth century when attempts at operative cure were made which rarely succeeded.

It was not until 1852, when Sims (1) published his epoch making paper demonstrating his successful technic, that this distressing condition was no longer considered incurable and its treatment was placed on a sound basis. The work of Emmet (2), Simon (3) and Bozeman (4) contributed still further to the successful treatment.

In 1894 a great advance in the technic was made by Mackenrodt (5) who developed the method of a wide separation of the vaginal wall from the bladder on all sides of the fistula, so as to avoid tension, and the separate suturing of the vaginal wall and bladder. This flap splitting technic was the outcome of the suggestions of Martin, Sanger, Fritsch and others. Mahfouz (9), however, has called attention to the work of Colles (6) of Dublin who in 1861 split the vesico-vaginal septum and sutured the two layers separately, thus anticipating the development of the flap splitting technic by over thirty years.

The abdominal approach was first advocated by Trendelenberg (7). He opened the bladder suprapubically, while von Dittel (8) employed the suprapubic transperitoneal route. The vaginal route remains nevertheless the preferable approach, and is certainly safer than the abdominal route, which should be reserved for selected cases that are inaccessible due to fixation by scar tissue to the adjacent structures. The flap splitting technic is the basis of the modern operative procedure in use today. That method and the classical Sims technic are most generally employed.

The difficulties encountered in curing these cases are frequently so great and so varied that the personal experiences of the operator should be recorded as they may be of value as a guide to others. No two cases are exactly alike, and frequently modifications of technic must be improvised to meet the requirements at hand.

A review of some 41 cases of urinary fistulae, upon whom I have operated, and on which I have completed follow-up records is herewith submitted:

Total cases reported, 41

Cured, 30 or 73+ per cent

<sup>1</sup>The illustrations in the article are reproduced by courtesy of Surgery, Gynecology & Obstetrics.

- Failures, 5
- Definitely improved, 6
- Result of obstetrical injury, 17
- Postoperative injury, 22
- Of congenital origin, 2
- Complicated by cervical carcinoma, 7
- Complicated by sarcoma of cervix, 1
- In the inaccessible class, 19
- Schuchardt incision employed, 19
- Sims classical technic, 8
- Flap splitting operation and my modifications of it, 31
- Charles Mayo technic, 4
- Victor Bonney technic, 1
- Multiple operations, 23
- Vesico-urethral injuries, 6
- Ureteral fistulae, 2
- Complete destruction of urethra, 4
- Implantation of ureter into bladder, 1
- Resection of enormously dilated ureter and nephrotomy with cervico-ureteral fistula, 1
- Artificial fistula for drainage which would not close, 1
- Vesico-vestibular fistula, 1

The 5 failures were as follows:

1. Mrs. M. D., age 45, a postoperative fistula 1 cm. in diameter at junction of bladder and urethra involving the vesical sphincter. Had had three previous operations. I operated three times, flap splitting, Sims, and Mayo technic. The patient refused further operation.

*Note:* I should have used an artificial fistula for drainage either above or below.

2. Mrs. A. K., age 74, adenocarcinoma of corpus uteri. Had been treated with radium and panhysterectomy. A postoperative inaccessible fistula of 1 cm. in vaginal vault resulted. An attempt had been made to close it with failure. I operated with a Schuchardt incision and modified flap splitting technic with failure. Patient died of carcinoma five years later.

3. Mrs. F. S., age 20, adenocarcinoma of corpus uteri. Had been treated with radium and panhysterectomy with resulting postoperative inaccessible fistula in vaginal vault, 1 cm. in diameter. An attempt had been made to close with failure. I operated twice with Schuchardt incision and modified flap splitting technic with failure. Extremely difficult case.

4. Mrs. W. C., age 72, sarcoma of cervix. Treated with Percy cautery technic and ligation of internal iliacs. An inaccessible vesico-vaginal fistula 1½ cm. in vaginal vault resulted. A Schuchardt incision was made. On account of dense scar tissue, the result of the cauterization, making flap dissection very difficult and unsatisfactory, failure resulted.

5. Mrs. C. M., age 39, had had a panhysterectomy two years previously with resulting fistula in vaginal vault. Four operations were done in Chicago with failure, one of which was by the abdominal approach. There were two fistulae in the vaginal vault, 1½ cm. and ½ cm. I operated with a Schuchardt incision and a modified flap splitting technic. The operation was extremely difficult and resulted in failure. The patient failed to return for a further trial.

Six cases were classed as definitely improved because of a great change for the better from the original condition, the majority with only a slight leak. They were as follows:

1. Mrs. D. A., age 41, weight 222 pounds, had a 12 pound stillbirth which caused a large fistula involving the anterior vaginal wall from cervix to urethra, 5 cm. in length. The cervix was split transversely and the upper angle of the fistula terminated at the internal os. The patient was first treated for erosions and the phosphatic deposits removed. I operated three times, each time with an improvement. The first attempt was a flap splitting technic with healing except at the upper angle in the cervical laceration. In the second operation I dissected the cervix from the bladder above the fistula, closed the small opening and utilized one-half of the cervix to cover the site of the fistula. Four months later there was a recurrence of the opening just above the urethra. I closed the upper injury with catgut and silver wire and used the Mayo technic for the lower opening. The result was nearly perfect but there was leakage at times from the upper angle when the bladder was distended. The patient was greatly improved over the initial condition.

2. Mrs. B. T., age 37, had a labor with a transverse position and forceps operation which resulted in a fistula that extended as a sinus alongside of the urethra from the internal meatus to the vestibule where it opened to the left and below the external meatus. I operated twice. The sinus was dissected out from the vestibule to the bladder, where it involved the vesical sphincter. It was closed in layers with catgut and silver wire. The fistula was entirely healed but she had stress incontinence. In the second operation I used a Kelly suture to reinforce the sphincter with improvement. A pessary helps control the incontinence.

3. Mrs. A. M., age 31, after a high forceps operation developed a fistula 1 cm. in diameter in the midline of the trigone. I first did a typical flap splitting operation with catgut and silver wire, but a small pinhole opening recurred. I then employed Victor Bonney's technic, which is a sliding flap operation, with an apparent cure. Some months later she reported there was some slight moisture present. My impression is that the purse-string suture used in the Bonney technic caused tension in this case, and that interrupted sutures would have been better. She refused further operation.

4. Miss A. Q., age 24, wet all her life, had a congenital malformation of a double urethra. An accessory urethra 2 inches in length extended from an opening in the bladder alongside the normally situated urethra and opened in the vestibule to one side and below the normal external meatus. At the first operation a grooved director was passed through this urethra into the bladder and it was incised. The mucosa was removed and the tract obliterated with sutures. Incontinence still continued and examination showed no vesical sphincter control in the remaining urethra which was defective for one-third of its length. At the next operation the margins of the defect were freshened and sutured around a small catheter and Kelly mattress sutures placed at the site of the sphincter. A definite improvement was obtained.

5. Mrs. M. I., age 23, came under my care at the Woman's Hospital in October, 1920 with complete urinary incontinence, dating from December, 1919 when she had a full term baby delivered by craniotomy. Examination showed a vesico-vaginal fistula at the site of the trigone and with complete loss of the urethra, as large as a 25 cent piece. There was dense scar tissue in the vaginal vault and on both side of the pubic arch, making the base of the bladder and the anterior vagina and cervix firmly fixed. The posterior vagina also was full of scar tissue. The patient was very short and very obese, weighing over 200 pounds.

On October 26, 1920 I operated as follows: A Schuehardt incision was made extending from the vault of the vagina to the coccyx. Incisions were then made through the scar tissue of the vaginal vault to the subpubic arch, and on either side of the site of the urethra thus loosening the tissues in order to allow approximation of the margins of the fistula without tension. The vaginal edges of the fistula were dissected free from the bladder for one-half an inch and the bladder opening united with interrupted No. 1 tanned gut sutures.

Silkworm gut sutures closed the vagina, and incisions in the scar tissue were closed in reverse direction with catgut. A self-retaining catheter was inserted, and the Schuchardt incision was closed. No attempt was made to construct a urethra.

On November 23, 1920 it was found that the fistula was now reduced to a diameter of about one-quarter inch and was just posterior to the site of the internal meatus. The margins of this opening were denuded and interrupted sutures were passed to narrow the orifice in the hope of increasing the vesical control. The result of the operation was partially satisfactory, as the patient could remain dry while in the recumbent posture. The next operation was done on January 9, 1922, when an effort was made to construct a urethra.

There was an entire absence of urethra around the neck of the bladder at the site of the internal meatus. A scalpel was used to undermine the edges of each lateral wall of the superior urethra that remained, and the loosened flaps thus obtained were made to encircle a small rubber catheter which was passed into the opening in the bladder, and the edges were united with tanned gut sutures. The edges of the anterior vaginal wall were then brought together over the new urethra with silkworm gut sutures. The result of this operation was a complete failure as the tissues sloughed away, and the patient was discharged in the same condition as on her second admission. She was admitted to the hospital for the third time on October 25, 1922, and I operated on November 8, 1922, and the result was most satisfactory.

In the first attempt I was guided by the method successfully employed by Noble, and in studying the problem at the second operation I determined to try the technic of Kelly, of making a tunnel under the vestibule and drawing through it a long flap, dissected from the anterior vaginal wall with its end left attached to the vesical opening. I had grave doubts as to my being able to employ this ingenious procedure, because the anterior vaginal tissues from which I should have to obtain this flap were so thin, and were made up largely of scar tissue as a result of my original operation for the closure of the extensive defect in the trigone of the bladder. My fears were justified, as after I had succeeded in dissecting up a flap sufficient for my purpose, I had exposed the bladder wall underneath which was so extremely thin that it was not possible to leave it to granulate, and neither was it possible to approximate the lateral edges of the vaginal wound as the denuded surface was too wide.

Noble has suggested the use of the labium minus as an attached flap in this region, so I employed this tissue to cover the denuded and weakened area at the base of the bladder. After making a tunnel behind the original site of the urethra and drawing the vaginal flap through it and suturing it in place, I incised the inner surface of the right labium minus at its attachment to the vestibule from the region of the clitoris to its base and then unfolded it by dissection. This gave an ample flap attached by a broad base which was easily brought in place over the denuded area of the vaginal wall and was sutured in position with silkworm gut. A small soft rubber catheter was inserted in the new urethra and fastened with a suture.

The tissues healed without difficulty and the result was most satisfactory as the patient was dry in both the recumbent and erect posture and she can urinate without difficulty. We were particularly fortunate in establishing a good control in this case, probably due to some reenforcing sutures placed at the neck of the bladder at its junction with the new urethra. Four years later she reported that she had slight leakage. Examination disclosed two pinpoint openings alongside the reconstructed urethra. She refused further operation as her condition was greatly improved over her original state. (figs. 1, 2, 3, 4, 5, 6, 7).

6. Mrs. M. S., age 29, came under my care at the Woman's Hospital in May, 1919, complaining of complete inability to hold the urine since an instrumental delivery 4 years previously. On December 8, 1915, when 6½ months pregnant with twins, the membranes ruptured spontaneously and an instrumental delivery was performed. On the seventh day postpartum urine flowed continuously from the bladder. Two months later an unsuccessful attempt was made to close the opening in the bladder, and in the following 4 years thirteen unsuccessful attempts were made by three different surgeons. Three years

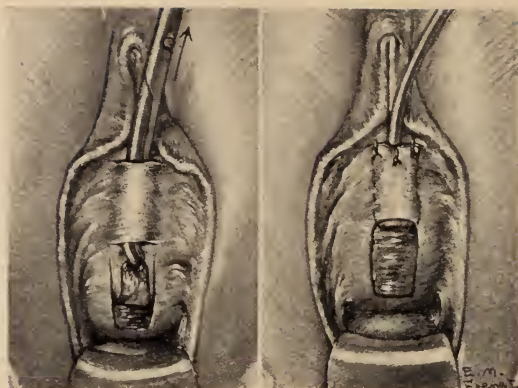


FIG. 1

FIG. 2

FIG. 1. Drawing the flap through the tunnel to form the new urethra.  
 FIG. 2. The flap sutured to the upper opening of the tunnel and a small catheter inserted into the bladder to maintain the patency of the new urethra.

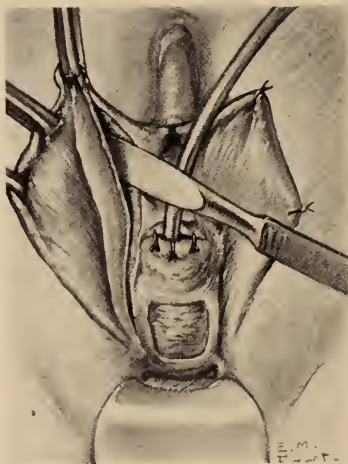


FIG. 3. The denuded area on the anterior vaginal wall is extremely thin as the flap was procured from the scar tissue of the previous operation for closure of the defect; therefore it requires reinforcement. The right labium minus is put on the stretch and an incision made throughout its length on its inner surface opening its folds.

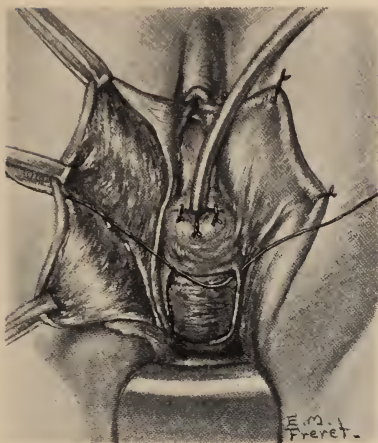


FIG. 4. The dissection unfolding the labium minus complete, and the first suture passed



FIG. 5. Completing the suturing of this attached flap to the defect at the bladder base

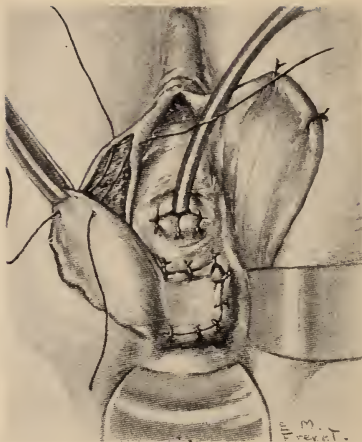


FIG. 6. The denuded area of the vagina and the bladder completely closed with the attached flap and sutures passed to close the upper angle of the incision.

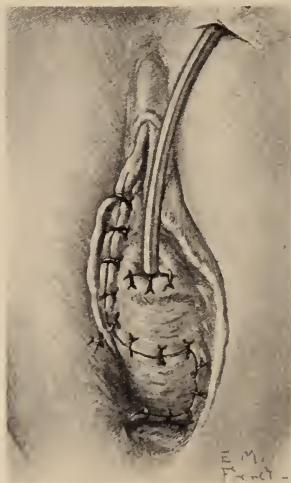


FIG. 7. The completed operation

ago, during one of the attempts, an abdominal hysterectomy was done, but for what reason it has not been possible to ascertain.

The patient was a well developed woman, weighing 150 pounds. The examination showed the external genitals and the vagina to be edematous, red and excoriated, with numerous phosphatic deposits embedded in the tissues. The entire anterior vaginal wall was absent, the base of the bladder being completely gone with the ureters opening into the vagina. The urethra was absent with the exception of a small thin quadrangular flap of tissue one-half to three-quarters of an inch in length which hung dependent from the vestibule and which was perforated by the external meatus. The cervix had apparently been amputated at some time independently of the hysterectomy, evidently a supravaginal operation, as a stump could be palpated above the flush vaginal vault. The pelvic floor was moderately relaxed.

The patient was kept in bed and treated by means of hot douches and boroglyceride packs. Zinc oxide ointment was used externally. The patient was given the preparation used by Dr. Thomas Addis Emmet to render the urine acid and to prevent the formation of phosphatic deposits: 1 dram benzoic acid, 2 drams sodium borate in 8 ounces of water, given in water, one tablespoonful three times a day, and reduced to 1 dram after 4 days.

The removal of the phosphatic deposits was an extremely painful process. It was necessary repeatedly to anesthetize the patient to allow of this being done. This course of preparatory treatment lasted for 6 weeks when the inflammation finally subsided. On July 7, 1919, the patient was operated upon. She was placed face downward in the reverse Trendelenberg position, with the hips markedly elevated. A large vaginal retractor was inserted and the perineum retracted upward. This position insured a complete ballooning of the vagina and of the bladder and allows the blood to run into the bladder, thus facilitating the operative work. I consider this posture of the greatest value in this type of case, and that it is one of the prime factors in the result obtained.

The ureters were probed to establish their location. With scissors a strip of tissue from one-half to three-quarters of an inch wide was excised completely around the edges of the cavity, extending on the inner surface of the quadrangular flap at the site of the urethra. The cervical stump was grasped with a bullet forceps and traction toward the urethra made easy the approximation of the tissues lateral to the cervical stump, throwing the margins of the fistula into angles in the lateral fornices, so that the fistulous opening originally shaped like the letter O now became shaped like the letter U.

The vesical edges of each angle were then closed by interrupted sutures of No. 1 tanned catgut. A second layer of interrupted sutures of silkworm gut was passed through the vaginal mucosa and the denuded area on both sides, and the ends left long and tied together. The quadrangular flap at the site of the urethra was placed over the denuded stump of the cervix and sutured in a similar manner. The result of this operation was a complete closure of the defect without tension.

A self-retaining catheter was inserted through the urethral meatus and the bladder was washed out with boric acid solution. Care was taken to wash out the catheter daily. It was retained for 12 days, at which time the sutures were also removed. The wound healed by primary union and is entirely closed except a small pinpoint opening on one side of the meatus. The result was most satisfactory; although the patient has no vesical sphincter she is able, in erect posture, to retain the urine without leakage for a period of 2 hours; at night she can go more than 4 hours, depending upon the quantity of urine being excreted.

In the past years she occasionally returns because of the formation of phosphatic deposits and irritation, due to the fact that she gets careless about keeping her urine acid, which she is instructed to do by taking appropriate medication. When her urine becomes acid the irritation subsides and she is greatly improved over her original terrible condition. (figs. 8, 9, 10, 11, 12).

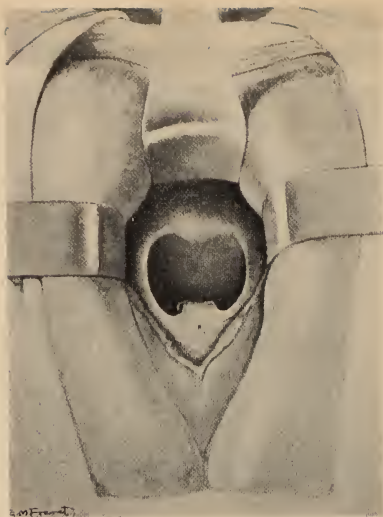


FIG. 8. Showing loss of tissue in vesico-urethro-vaginal fistula

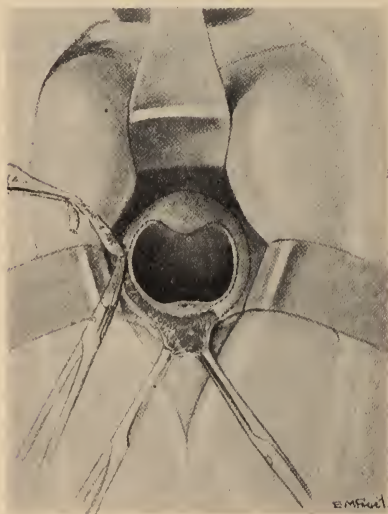


FIG. 9. Excision of strip of tissue around edges of cavity

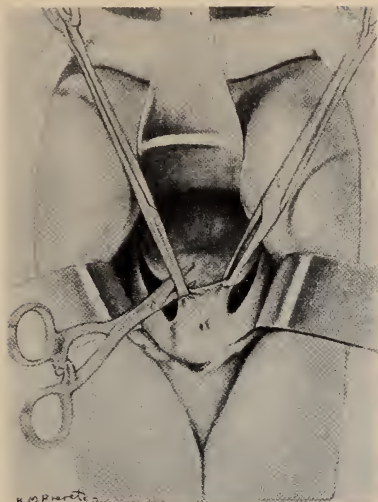


FIG. 10. Traction applied with bullet forceps to cervical stump and toward urethra changing fistulous opening from O to U shape.

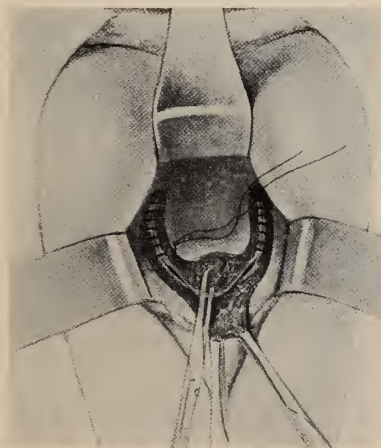


FIG. 11. Edges of denudation closed by interrupted sutures of No. 1 catgut, and silk-worm-gut sutures.

Cases which were of unusual difficulty, due to various complications and in which a perfect cure was obtained, may be mentioned in detail. The following five cases had carcinoma of the cervix treated by radium or cautery in which an inaccessible fistula developed either from the treatment, or the disease.

1. Miss M. J., age 34, was treated by me for carcinoma of the cervix Class III in February, 1927. The disease had destroyed the anterior half of the cervix and was invading the wall of the bladder. 4200 mg. hours of radium were given. The patient did badly and became cachectic and entered the House of Calvary as a hopeless case in June, 1927. She remained there until February, 1928 when she returned to the clinic looking and feeling well, having regained her normal weight, but complaining of incontinence of urine. Examination showed no evidence of carcinoma present, but a vesio-vaginal fistula 2 cm. in diameter in

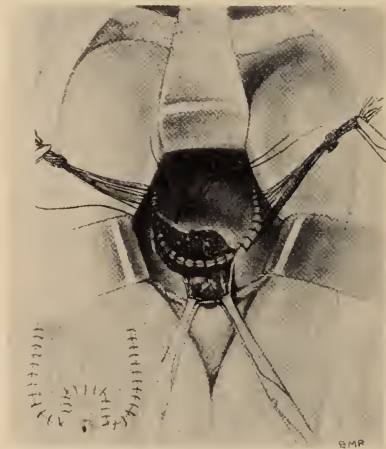


FIG. 12. Quadrangular flap at site of urethra sutured over the denuded cervical stump

the anterior vaginal fornix. I operated on February 9, 1928. The vagina was atrophic and contracted. I made a Schuchardt incision and did a flap splitting operation commencing the incision near the urethra to obtain the plane of cleavage, and displaced the bladder downward with a straight sound passed through the urethra. The fistula was closed transversely with two rows of catgut and the vagina closed with silver wire sutures. The fistula healed per primum and she has been well ever since. I last saw her in September, 1941, fourteen years after the treatment for carcinoma, with no evidence of recurrence and perfectly dry.

2. Miss E. L., age 50, first came under my care in September, 1902. She was 47 years of age. Examination disclosed well advanced epithelioma of the cervix. No macroscopic involvement of the broad ligaments or vaginal vault could be determined. On September 12, 1902, I opened the abdomen and removed the uterus and adnexa by an ordinary panhysterectomy. I also cauterized the cervical site with the paquelin cautery. The patient made a speedy recovery, but returned, not unexpectedly, seven months later with a re-

currence of the disease in the vaginal vault. Examination showed a nodule the size of a walnut on the posterior surface of the bladder and base of the broad ligament. On April 10, 1903, I reluctantly operated, removing the nodule, after opening the vaginal vault. I then cauterized the whole of the area, having in mind the proximity of the bladder. This was before the days of the Wertheim operation or radium. The cautery undoubtedly saved this woman's life, but at the expense of her bladder, as a few days after the operation she developed a vesico-vaginal fistula which opened into the vault. The patient would not consent to an attempt at closure of the fistula until May, 1906. The fistula presented a small opening at the top of the vagina, and with the patient in the Sims position, an attempt to close it was made by making a crucial incision and a dissection of the vaginal flaps at the site of the fistula, but the exposure was unsatisfactory and the vaginal route was abandoned for the suprapubic. The fat abdominal wall and the adhesions of the rectum and posterior surface of the bladder, the result of the extensive cauterization at the previous operations, compelled an abandonment of this method, as decidedly less advantageous than the vaginal route in this case. So a return was made to the original operation, and the fistula closed very imperfectly, as shown a few days later when a complete failure resulted.

In May, 1909 she returned to me in good health and showing no evidence of recurrence whatsoever. Her condition was pitiable, however, her thighs and external genitals were excoriated and in a distressing state due to the constant dribbling of urine. She had been unable to retain her position in a department store owing to the uriferous odor, and she was ready to again try for relief. The vagina was markedly contracted and the tissues were less elastic than at the previous operations, and the case was less favorable than before. I made deep paravaginal incisions in each vaginal sulcus, severing the anterior fibres of the levator ani muscle. This rendered the vaginal vault more accessible. I then made an incision from just below the external meatus up the midline of the anterior vaginal wall to the fistulous opening in the vaginal vault and continued this incision on the posterior vaginal wall for about 2 cm. beyond the fistula. A transverse incision was made at right angles to the above. The separation of the anterior vaginal wall from the bladder was then begun at the outer end of the incision just posterior to the external meatus. The line of cleavage between the bladder wall and the lower vagina was easily found, as it was free from adhesions, then when this was established, it was comparatively easy to follow up this plane to the region of the adhesions, and it allowed of their separation, with a fair degree of safety until the bladder was completely loosened from the vaginal vault. It is important to make the lateral dissection of the bladder as wide as possible at the vault to insure success in the next step, which was to dislocate the bladder downwards and outwards through the incision in the anterior vaginal wall. I utilized a straight male sound, No. 28 French, which was passed into the bladder through the urethra and used as a lever to displace the organ. The fistula was thus made easily accessible and the opening was closed with interrupted No. 1 chromic catgut sutures. These sutures penetrate the muscular coat of the bladder only and have the effect of turning in the edges of the fistula. The vaginal incision was then closed with silkworm gut sutures, being careful to catch the base of the bladder to one side of the line of sutures closing the fistula, in order to avoid the dead space and to bring the lines of suturing in different positions. The paravaginal incisions were then sutured and a self-retaining catheter inserted. The result was perfect and remained so for eleven years when I last heard from her. (figs. 13, 14, 15).

3. Mrs. H. W., age 34, was admitted to my service at the Post-Graduate Hospital in March, 1909 with epithelioma of the cervix. This patient was very fat and difficult to examine. As the uterus was movable, it was thought that she might be given the benefit of a radical operation. I accordingly opened the abdomen and did a panhysterectomy, making an extensive dissection of the ureters, and removed as much of the broad ligament and vaginal tissue as possible after the method of Wertheim. In dissection out the right ureter I found it completely surrounded with a carcinomatous nodule where it entered the bladder. As this nodule involved the bladder, I deemed it best to resect that portion of the bladder wall just superior to the insertion of the ureter. I closed this rather large opening

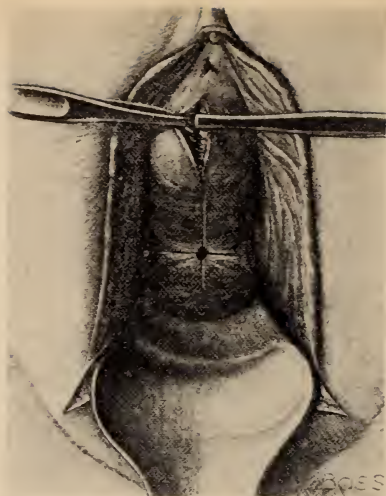


FIG. 13. Commencement of mobilization of the bladder



FIG. 14. Displacement downward of the bladder by means of a sound and sutures placed in fistula.

in the bladder with chromic catgut sutures and provided vaginal drainage. The patient made a good recovery, but was left with a vesico-vaginal fistula in the cicatrix of the vaginal vault. Seven months later she returned to have the fistula closed. She had gained in weight and was feeling well, but there were undoubted evidences of induration in the vault, showing a recurrence of the disease. I operated purely with the idea of making her comfortable during the few months she would have to live, and I adopted the same plan of operation as in the previous case. The patient had a perfect result so far as the cure of the fistula was concerned.

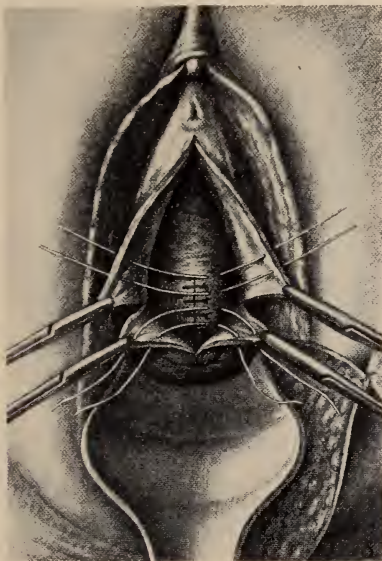


FIG. 15. Vaginal sutures *in situ*

4. Mrs. C. M., age 53, in April, 1915 was referred to me with carcinoma of the cervix, the parametria apparently not involved. The case was suitable for a Wertheim operation, but as she was excessively obese and her general condition poor, the Percy cautery technic was employed. The abdomen was opened and the uterus held by an Assistant while the tissues were cooked with the cautery iron for one hour with a low heat. In September, 1916, one year and five months later, she was feeling well with no symptoms or evidence of carcinoma, but she had an inaccessible vesico-vaginal fistula in the vaginal vault in dense scar tissue. I operated on September 25, 1916. A Schuchardt incision was made as the vagina was small, and the modified flap splitting technic I employ was used. The fistula was closed with catgut and the vagina with silkworm gut. When the sutures were removed on the fifteenth day a slight leak appeared and the catheter was reinserted for 5 days. On its removal she was perfectly dry, and remained so. She was perfectly well for several months while under our observation when we lost trace of her.

5. Mrs. M. S., age 50 in 1927 was radiated elsewhere for advanced carcinoma of the cervix. In February, 1930 she came under my care with an inaccessible vesico-vaginal fistula in the vault, and there was an indurated mass involving the entire anterior vaginal wall, which was at first thought to be recurrent carcinoma. A sound in the bladder showed that the hard mass was a calculus the size of a plum. This was removed through an incision of the anterior vagina, and the bladder washed out. While the fistula was sutured there was little expectation of a cure on account of the infection present. The cystitis was treated, and on the infection being overcome an attempt to close the fistula was made in May, 1930 as there was no evidence of carcinoma. A Schuchardt incision and the modified flap splitting technic, as previously described, was done but was a complete failure.

In February, 1931 the above technic was repeated again with a failure. In December, 1931 I made a third attempt, using four stay sutures as tractors, and dissecting out the entire scar tissue around the fistula, and separating the bladder more widely than before, using catgut for the fistula and silver wire for the vaginal incision, this time with a perfect result. She remained dry for  $2\frac{1}{2}$  years when she developed a recurrence of the carcinoma and died  $6\frac{1}{2}$  years after her radiation.

The failures of the operations in this case were undoubtedly due to the lack of vascularity in the scar tissue caused by the radiation, and my failure to completely remove the cicatrix.

The following cases were of unusual difficulty and interest:

1. Mrs. C. R., age 37, weight 280 pounds, came to me in March, 1921 with a small vesico-vaginal fistula under the left ramus of the pubis densely adherent to the bone, with a displacement of the urethra to the right side. This was the result of a pubiotomy done for a contracted pelvis. Three attempts at repair had been made with failure. I did a difficult flap dissection closing the opening transversely with a failure. Two months later I resected the fistulous tract and scar tissue and closed the layers with catgut and silkworm gut with a successful result. She remained perfectly dry for nine years when she returned with leakage caused by phosphatic calculi which had ulcerated through the scar. There were three small openings, and I removed a stone the size of a cherry and several smaller ones, which were between the bladder and vaginal wall. The bladder was left open for drainage to treat the infection, but she refused further operation.

This case shows the importance of keeping the urine acid and free from infection after these operations. I have had several similar experiences and always warn these patients to test the urine with litmus paper and to keep the urine acid with acid sodium phosphate as required.

2. Mrs. W. P., age 36, was referred to me in January, 1934 with a vesico-urethro-vaginal fistula, the result of a 14 pound stillbirth with hydrocephalus. There had been sloughing of the vaginal mucosa so that the vagina was markedly contracted with a cicatricial ring. The fistula, 1 cm., was at the site of the junction of the urethra and bladder with destruction of the upper half of the urethra. I first operated to close the fistula, the reconstruction of the urethra being deferred for a later attempt. A Schuchardt incision was made and the cicatricial ring incised on either side. The vesical fistula was closed by the Sims technic with silver wire sutures. A flap dissection was inadvisable due to the scar tissue. The result was successful in closing the bladder defect.

The reconstruction of the urethra was attempted four months later. The opening into the bladder was now only one-eighth of an inch in size. A U shaped incision was made encircling this opening and the urethral margins dissected and sutured around a small catheter. A Kelly mattress suture was placed at the site of the sphincter and the vaginal flaps closed over the urethra with silver wire. The result was not satisfactory for control of the urine, although improved.

Five months later I used the Martius technic of suturing the bulbo-cavernous and ischio-cavernous muscles under the urethra. This operation was a perfect success and has remained so for over eight years.

3. Mrs. E. D., age 43, was referred to me with a urinary fistula in the vault of the vagina following a complete hysterectomy in June, 1928. Cystoscopy and x-ray disclosed that the bladder was not involved, and that the right ureter had been severed and was discharging into the vagina. I operated in February, 1929. The abdomen was opened and I dissected the ureter from the scar tissue of the vaginal vault. The ureter was enlarged to the size of a finger. The bladder was separated from its lateral attachments, and a small opening was made in the fundus. The end of the ureter was split and passed into the bladder, and the split ends sutured with mattress sutures of catgut through the bladder wall. The margins of the bladder opening were sutured to the ureter, which was covered with peritoneum. A drain was placed, and the abdomen closed. A perfectly functioning ureter was demonstrated by the cystoscope one month later.

4. Mrs. E. T., age 27, came under my care in January, 1934 with the history of a profuse, semipurulent, foul discharge for the past three months following a curettage after a six months premature labor. She had had a three months miscarriage in 1931, and after an unsatisfactory attempt at curettage to stop the bleeding, the abdomen had been opened and a cordiform uterus was found with a septum, in the left side had been the seat of pregnancy. The fundus was opened, the contents removed, and the septum divided. She became pregnant again in 1933 and had a six months premature labor after which she was curetted for discharge, but no tissue was obtained and profuse bleeding and clots followed.

Examination disclosed several congenital developmental malformations. The anus was situated in the perineum, there were defects in the sacrum and in the upper ribs. The fundus uteri was displaced to the right side and of normal depth. The left side of the pelvis was filled with an ellipsoidal cystic mass extending to the umbilicus. On a second examination, to our surprise, no mass was felt, and as subsequently it was found again and the purulent discharge from the cervix was intermittent, a tentative diagnosis of an hydrosalpinx was made.

Cystoscopy revealed a congested bladder with normal capacity and the right ureter gave a free flow of clear urine. The left ureteral orifice could not be located. Skiodan pyelograms revealed a normal right kidney and ureter, and was entirely negative on the left side. Tests of the cervical discharge revealed urinary elements, and the diagnosis was then made of a uretero-cervical fistula resulting from the postpartum curettage which evidently perforated the uterine wall and the ureter.

On January 31, 1934 I did an exploratory laparotomy and found the ureter adherent to the left side of the cervix and the size of the index finger. Three inches upward it expanded into a large globular cyst the size of a grapefruit, and above it divided into two parts which were inserted into a double kidney pelvis. The kidney was enormously enlarged. The uterus was cordiform in shape, and there was a bilateral salpingo-oophoritis with adhesions. I split the posterior peritoneum, ligated and dissected out the hydro-ureter, which was distended with foul purulent urine, and placed two cigarette drains. I removed the adherent tubes. The kidney was left for subsequent removal.

The patient had a stormy convalescence with acute peritonitis. She got out of bed on the fifth day, February 6, 1934, and completely disrupted the abdominal incision. Dr. Arthur Murphy, under local anesthesia, resutured the wound with through and through sutures and at the same time did an ileostomy on a distended loop of the ileum inserting a catheter and cigarette drain. A posterior colpotomy was done later for drainage. The patient made a slow but good recovery and was discharged on April 19, 1934 to return later for removal of the kidney.

On June 5, 1934 Dr. Murphy and I operated doing a nephrotomy through the usual kidney incision. We found the kidney to be a densely adherent sac full of purulent necrotic tissue. This was opened and the contents evacuated and drainage inserted. She made a complete recovery and was discharged on July 28, 1934. She was last seen in December, 1935 perfectly well.

5. Mrs. E. H., age 26, married 6 years, was referred to me with the history of having had one labor in September, 1928, at full term. A difficult forceps delivery resulted in a dead

baby, a vesico-vaginal fistula and loss of the urethra. She had been operated upon eight times during the past 4 years, all operations ending in failures. The last operation was in June, 1931.

I first saw her on June 6, 1932, and my examination showed a complete loss of the urethra with the exception of the external meatus, and a vesico-vaginal fistula circular in shape and with a diameter of 1 cm. situated in the trigone near the site of the internal meatus. On November 22, 1932, I operated as follows:

An incision was made on the anterior vaginal wall above the fistula outlining a quadrangular flap 2.5 cm. wide and 3 cm. long. This flap was dissected from the vaginal wall up to the fistula leaving it attached with the upper margins slanting obliquely to the superior border of the vesical defect. The flap was then formed into a tube by suturing the margins together after the technic suggested by Dr. Farrar. A soft rubber catheter was then passed through this tube and into the bladder through the fistula. The site of the original urethra was then dissected out so as to form a deep U shaped groove and the newly constructed tube was laid in this groove and its end with the catheter was brought out of the external meatus, and sutured to it. The margins of the groove were then brought together over the urethral tube and sutured with interrupted sutures. A Kelly mattress stitch of linen was then placed at the neck of the bladder for control and the edges of the vaginal denudation were united with interrupted sutures.

The wound healed by primary union with a perfect restoration of the urethral canal and closure of the fistula. For a few days the patient had some control of the bladder, but when on her feet the control was insufficient so that in the erect posture it was unsatisfactory. I found that slight pressure on the urethra completely stopped the flow of urine, and I succeeded in obtaining a satisfactory control by using a Thomas-Hodge pessary inserted in the *reverse* position. The exact amount of necessary pressure on the urethra was easily obtained by softening the pessary in boiling water and bending the bulbous end to the required angle. The patient is perfectly dry and comfortable with the pessary, and she removes it for cleansing and replaces it herself whenever necessary. However, at times the pessary would get out of place, due to the lacerated pelvic floor, so in June, 1933 I repaired the rectocele and pelvic floor, since which time the pessary remains *in situ* and functions satisfactorily. In the meantime her husband left her and she remarried. She became pregnant in May, 1937 and on January 19, 1938 I did a low flap caesarian section as I did not consider it safe to allow of a delivery through the pelvis which would endanger the plastic work that had been done on the bladder and urethra. She was delivered of a 7 pounds, 2 ounces boy, and is perfectly well and happy today. (figures 16, 17, 18, 19).

Emmet carried on the pioneer work of Sims at the Woman's Hospital and had the most extensive experience with these cases of anyone of his time. He reported some 270 cases, 200 of whom were cured, or approximately 70 per cent. He classed 50 or 60 as improved and 5 as incurable. He stressed the importance of preliminary preparation of the patient and of making vaginal incisions to relieve tension when necessary, and considered this was "the secret of success."

Undoubtedly the man who has had the greatest experience in our time is Dr. N. Mahfouz, Professor of Gynecology in Cairo, Egypt. Dr. Mahfouz now has the Egyptian title of "Pacha," while formerly he was a "Bey," and as their custom is to place the title after the name he has frequently been quoted in the literature as "Bey" instead of Mahfouz.

The incidence of vesical fistula is very high in Egypt as a sequel of neglected labor, and thus Mahfouz has had a vast experience with these cases. He reported in 1929 in the British Journal of Obstetrics and Gynecology, some 300 cases he had operated upon with an 87 per cent cure rate, and in his last 100 cases

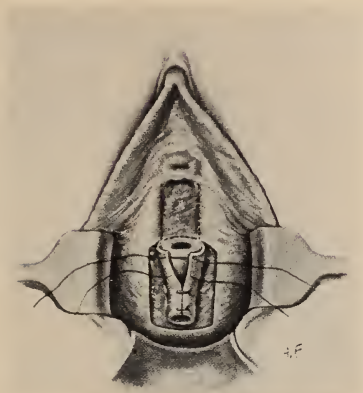


FIG. 16. Reconstruction of the urethra. The dotted line shows the site of the destroyed urethra with the external meatus intact and a vesico-vaginal fistula at the neck of the bladder. As suggested by Farrar the quadrangular flap dissected from the anterior vaginal wall and sutures passed to convert it into a tube. Note the upper margins of the flap end above the fistula.

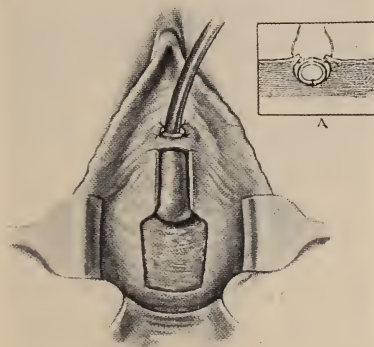


FIG. 17. A catheter is passed through the tube and into the bladder, and the new canal is laid in a deep U shaped excavation that has been made at the site of the original urethra. See insert A.

had cured 95 per cent. In 1938 in the same Journal he reported having operated upon over 400 cases in 30 years. Mahfouz advises spinal anesthesia as it gives

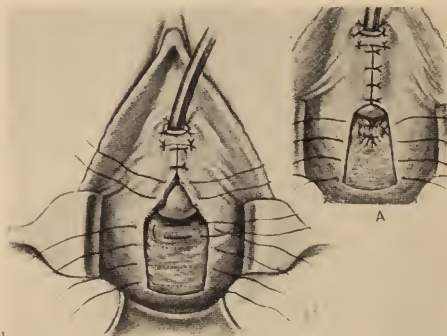


FIG. 18. The end of the canal sutured to the external meatus, and the margins of the excavation brought together with sutures over the new urethra. A mattress stitch (Kelly) is placed at the neck of the bladder. Insert A shows the mattress suture tied, and the sutures placed to close the vaginal denudation.

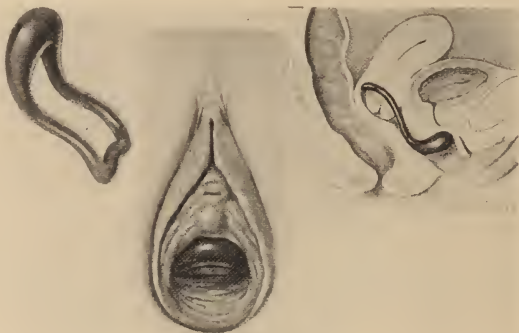


FIG. 19. Thomas-Hodge pessary placed in *reverse* position, the end having been bent to give the correct amount of pressure to insure vesical control.

relaxation of the pelvic floor. He stresses the importance of inverting the edges of the denuded fistula by proper placing of sutures. He uses catgut and silkworm gut, and warns against tying sutures too tightly. He uses small

round needles, and ties in a small straight catheter for drainage. In judging of cure rates, however, one must bear in mind that much depends on the type of case. The postoperative inaccessible fistula in the vaginal vault, those that involve the urethro-vesical junction, or destruction of the urethra, and those that follow radiation for carcinoma with formation of scar tissue, are more difficult to cure than many large fistulae situated in the trigone of the bladder.

In my experience the majority of cases seen have been the result of surgery, or radiation for carcinoma. Hysterectomy or radiation by those lacking operative skill and knowledge of gynecologic anatomy and technics are accountable



FIG. 20. Schuchardt's incision outlined

for many small inaccessible fistulae in the vaginal vault. I have found the Schuchardt incision, if properly made, a most valuable aid in overcoming inaccessibility (figs. 20, 21, 22).

I have stressed the importance of commencing the separation of the vagina and bladder in the lower vagina to establish the plane of cleavage where there is an absence of scar tissue, and of using a straight male sound passed through the urethra to displace the bladder downward, and thus bring the fistula within easy reach. Interrupted catgut sutures on short round pointed curved needles close the fistula inverting the edges, and silkworm gut, or silver wire, is used for the vagina, being careful to avoid dead space. I prefer a straight catheter tied in place for drainage.

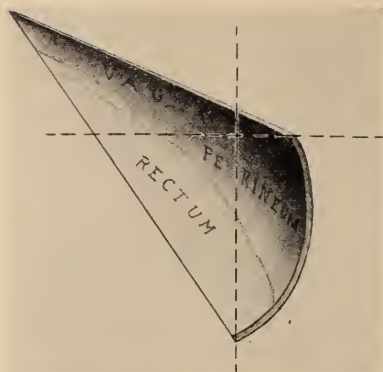


FIG. 21. Geometric figure of the plane of the incision



FIG. 22. Schuchardt's incision completed (drawn from life)

If the fistula is imbedded in scar tissue, the result of radiation or cautery, it is most important to dissect out this tissue, even if the fistula is enlarged thereby, as the lack of vascularity will be a cause of failure. When multiple attempts have resulted in failure with the flap splitting technic, I have found the Sims operation with silver wire sutures often successful.

Fistulae involving the internal vesical sphincter are often the most difficult cases to cure. While the fistula can be closed, control is absent because of the destruction of the muscle. Complete or partial destruction of the urethra can be remedied by the construction of a new urethra by using the technic suggested by Dr. Lilian Farrar (10). A self-retaining catheter should not be used in these cases. A small straight tied in catheter is less apt to prevent healing at the vesical neck. It is often wiser to secure drainage through an artificial fistula made in the trigone, or by a suprapubic cystotomy. Lack of control may be overcome by the excellent operation recently devised by Dr. Aldridge (17), of the Woman's Hospital, in which strips of the rectus fascia are brought down behind the symphysis and united around the urethra, or by the technic of Martius (18). Urethral fistulae should be closed transversely to avoid constriction.

In certain cases the reversed Trendelenberg position is of advantage in closing large fistulae. The posture allows a clear view of the operative field due to the distension of the vaginal walls, and bleeding is less troublesome as it runs into the bladder.

Rawls (14) technic of dissecting the pubo-cervical fascia from the vaginal mucosa and overlapping it gives additional security to the flap splitting operation.

Important points to remember before operating are that post-partum involution must be completed before attempting a repair, this will require at least two months, otherwise the tissues will be too soft. Small fistulae often close themselves if a retaining catheter is used *promptly* post-partum or postoperation. Infection of the bladder and tissues, and phosphatic deposits must be eliminated. The relation of the ureters to the field of operation must be determined. All tension of the tissues must be relieved before suturing the fistula. It is important to keep the urine acid after operation to prevent the formation of phosphatic deposits and calculi which may ulcerate through the scar of the operation. Time is necessary and painstaking care. Haste will cause failure. It is easier to cure a fistula with the first operation. Multiple operations that have failed greatly increase the difficulty of cure.

It should be remembered that no one procedure for the repair of vesical fistulae is adaptable to all cases. Each case is an individual problem and the type of technic must be selected, or improvised to meet the conditions present.

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## IDIOSYNCRASY TO AMMONIATED MERCURY

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Idiosyncrasy to ammoniated mercury may show itself in many ways; it may appear as a local eruption at the site of application of the drug, it may call forth a generalized eruption or it may cause not only manifestations referable to the skin, but involvement of the entire body, with severe symptoms due to cerebral, gastro-intestinal and renal involvement. The case history here to be described is an example of the severest type of sensitiveness to the drug. It is being reported because of the violence of the symptoms, the long course of the illness and the importance of correctly recognizing the drug idiosyncrasy as the causative agent.

### CASE REPORT

*History* (Adm. 493141). Joseph K., aged 5 years was first seen by me July 20, 1942. His past history was irrelevant. His only previous illness was varicella one year earlier. The present illness began ten days before when the boy complained of headache and malaise and a morbilliform eruption made its appearance on the feet and lower extremities, gradually spreading upward until the entire body became involved. The child did not appear very ill. He had a mild conjunctivitis but no cough or coryza. His physician at first thought the child was suffering from measles, a diagnosis which seemed corroborated by the appearance of an enanthem on the buccal mucosa. There was considerable headache and occasional vomiting.

When I first saw the boy he appeared to have a typical morbilliform eruption. His sensorium was clear. He had no catarrhal symptoms. The throat was slightly engorged and on the buccal mucosa there was a deep red enanthem, not as discrete as Koplik's spots. The ears were normal. The heart and lungs were normal. The abdomen was soft and the liver and spleen were not palpable. All the superficial lymph nodes were markedly enlarged, especially those in the groins and axillae. The nodes were discrete and not tender. There were no neurological signs. The genital organs were negative except that the right testis had not descended.

Since for many reasons the case did not seem to be one of measles, two other diagnoses were suggested, first, infectious mononucleosis, second, a toxic rash perhaps due to food or a drug. It was then ascertained that about June 20 (four weeks previously) the child had developed impetigo which had been successfully treated with 10 per cent ammoniated mercury ointment applied to the lesions for five days. I was assured that no mercury had been subsequently applied and for this reason was loathe to blame the condition on the drug since four weeks would seem too long a period of incubation. A blood smear was ordered to determine the presence of eosinophilia or possibly a blood picture of infectious mononucleosis.

I did not hear of the case for another week when I was asked to have the child placed under my care at the hospital. During the intervening week he had been seen by Dr. Isadore Rosen who had agreed that the disease might well be due to idiosyncrasy to ammoniated mercury and had finally succeeded in getting the child's nurse maid to admit that she had had the prescription of the ointment remade several times and had applied it to an eruption which had appeared on the child's chest on about July 10. She applied it in large amounts daily for seven days. During the week of July 20-27 the condition of the boy had become much worse and he was therefore hospitalized.

*Examination.* On arriving at the hospital the child's general condition was poor. He



cells, 24,000; segmented polymorphonuclear leucocytes, 37 per cent; non-segmented polymorphonuclear leucocytes, 33 per cent; monocytes, 3 per cent; lymphocytes, 15 per cent; eosinophiles, 12 per cent. Urea nitrogen, 25 mg. per cent. Total protein, 4.3 mg. per cent. Urine: specific gravity, 1006; albumin, faint trace; sugar, 0; occasional white cell; no casts. The stool was normal.

*Course.* A continuous intravenous injection of 5 per cent glucose in saline solution was at once started since the boy had taken no fluids for several days.

Lumbar puncture was considered but not performed for fear of introducing infection from the inflamed skin.

The child's temperature fluctuated, on the day after admission rising with a chill to 106°F. (fig. 1). Gradually with the use of starch baths, simple ointments externally and calcium gluconate and ephedrine by mouth, the child's condition improved on the third and fourth days. The urine showed a heavy trace of albumin with hyaline and granular casts and serious kidney involvement was feared. However, the urine cleared rapidly as the skin lesions became less angry looking and the temperature gradually came down to normal.

On August 10 the boy was discharged, his mental condition normal, the edema gone, the rash only represented by some dry desquamating areas, the urine normal.

#### COMMENT

Idiosyncrasy to ammoniated mercury is relatively common, though cases of great severity such as the one here described are rare. In 1934 Harper (1) called attention to this clinical picture reporting two cases in infants, one aged 16 months and one aged 20 months. Both these children were desperately ill and required hospitalization. In both cases 10 per cent ammoniated mercury ointment had been applied to impetigo lesions. In one case, "a generalized papulo-vesicular eruption on a thickened erythematous base" appeared a few hours after the application of the ointment. The feet became red, swollen and edematous, with desquamation before the condition of the skin returned to normal. In the second child symptoms did not appear until 9 days after the first application of the drug, when a macular rash appeared leading to the diagnosis of rubella. This child was acutely ill. The skin became extremely edematous followed by desquamation with many oozing crusted fissures. In this case also the hands and feet became greatly swollen, their color varying from blue to almost black. In both cases there was generalized adenopathy and the spleen was palpable. The second case was cured only after 30 days of illness. Harper commented on the paucity of reports in the literature.

In 1941 I published five cases of idiosyncrasy to ammoniated mercury including one of great severity (2). This concerned a girl aged six years who developed chicken pox; 10 per cent ammoniated mercury ointment was applied and five days later she developed fever of 105.2°F., unconsciousness, jactitation, severe general adenopathy, a deeply red erythema of the entire body with edema of the face and scalp and extreme pruritus. This was followed by desquamation and recovery in about a week. Before the correct diagnosis was made, the case was considered to be one of toxic scarlet fever.

Cases such as the above should be considered as suffering from sensitiveness to the drug and not to poisoning. None of the cases showed severe renal involvement nor did any have gingivitis or salivation. None of them were permanently damaged. Certain children may be sensitive to only one preparation

of mercury, others may react to many different compounds. Thus one of my cases had symptoms following the ingestion of Calomel, the application of one per cent yellow oxide of mercury ointment to a sty, the use of bichloride of mercury in a soap during an attack of varicella and finally from contact with metallic mercury itself. This child developed urticaria from the absorption of mercury from amalgam fillings.<sup>1</sup> The cases which showed very severe general symptoms appear to be those in whom very large amounts of mercury have been used (i.e., in one of my cases 6 ounces of 10 per cent ointment was applied within a few days). However, certain children are so susceptible that an unbelievably small amount of mercury may result in symptoms. In one of the cases reported by me, a school girl, known to have had several severe attacks of urticaria and edema resulting from the application of ammoniated mercury ointment, developed symptoms after attending a class in physics where she handled a glass funnel through which another student had poured metallic mercury. The small bits of mercury clinging to the glass were sufficient to cause symptoms of severe generalized urticaria twenty-four hours after her hands had come in contact with them.

The diagnosis of this condition depends mainly on obtaining an adequate history and having in mind the fact that sensitiveness to mercury may give rise to many different clinical pictures. In the cases in which severe generalized symptoms are present, one should remember that marked adenopathy may precede the pyrexia. Eruptions resembling measles, rubella or scarlet fever may precede the generalized edematous beefy red condition of the skin which is later followed by desquamation. Dryness and cracking of the epidermis with violent pruritus accompany this stage of the illness. The moderate splenomegaly and the general adenopathy may be confusing. Eosinophilia, often present may be of considerable diagnostic aid. One must not be misled by the presence of chills and high fever which seem to point toward the presence of infection.

Although in severe cases the condition of the patient appears grave, the prognosis is good. Renal damage does not seem to follow and the children quickly recover after the skin has returned to normal.

Treatment must be symptomatic. In the case here reported, intravenous glucose given at the height of the illness greatly improved the condition. For the extreme pruritus local applications do not seem to be of as much value as ephedrin given internally.

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## RELATIONSHIP OF HORMONAL ACTIVITY TO GASTRO-INTESTINAL DISEASES

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Experimental and clinical investigations point to a close relationship of hormonal activity to gastro-intestinal disease. The subject is so vast as to preclude any discussion of the entire gastro-intestinal tract. The stomach and duodenum will therefore receive consideration in a brief review.

One of the more promising findings is the action of the chalones on the volume and acidity of gastric secretion. A chalone is a hormone like substance which possesses an inhibitory action. Gray, Wieczorowski, and Ivy (1) recovered such a chalone from the urine of normal and pregnant dogs and gave it the name urogastrone. All gonadotropic factors as well as "the ulcer preventing factor of Sandweiss" were previously removed from the urine prior to investigation of the active factor. Injection of the substance into animals and humans caused a diminution in the volume and acidity of the gastric secretions. This action is similar to that of enterogastrone which can be isolated from the mucosa of the small intestine. Further confirmation of this relationship is found when removal of the small intestine in dogs is accompanied by the disappearance of urogastrone from the urine. That a relationship exists between the finding of urogastrone in the urines of female dogs and the high incidence of peptic ulcer in males (9:1 according to Abrahamson and Hinton (2)) is a strong possibility. The possible use of urogastrone, once chemically isolated and produced, in the treatment of peptic ulcer has been suggested by the work of Ivy and his group. Since the objective of all procedures in operative surgery for peptic ulcer is the change of gastric physiology especially the reduction of acidity, such accomplishment would be obviously preferable with nonoperative methods. On the other hand gastrin is a hormone which stimulates secretion of the stomach (Edkins (3)). This hormone is produced by the pyloric mucosa in response to the presence of food stuffs in this region.

It has been postulated that humoral factors from the brain play an integral part in the pathologic physiology of the stomach. The post-mortem findings of fresh gastric lesions following injury at the base of the brain have stirred up the hypothesis that neurogenic or hormonal influences from the hypothalamic area are associated with gastric ulceration. Sheehan (4) has demonstrated that the hypothalamus is the center for the autonomic nervous system, the posterior and lateral portion being concerned with the origin of the sympathetic impulses while the anterior portion is associated with parasympathetic impulses. Stimulation of the former causes delay of activity and emptying of the entire gastro-intestinal tract and rise in blood pressure, while stimulation of the latter produces increased activity of the gastro-intestinal tract with either an immediate reaction or a delayed or hormonal reaction. Further, the hypothalamus may

act through the pituitary as an intermediary since it is known that injury to the former area will decrease the antidiuretic hormone output of the pituitary gland and result in diabetes insipidus. It is, however, the considered opinion that a direct relationship between the hypothalamus and peptic ulcer has not been established. This is borne out by two salient features: 1) In hypothalamic lesions there are multiple small, acute erosions or small ulcerations of the gastric mucosa in contrast to the one or two large ulcers found in clinical peptic ulcer; 2) the ulcerations of hypothalamic origin are found throughout the gastric mucosa in contrast to the frequency of peptic ulcer along the lesser curvature.

One of the most interesting clinical features of peptic ulcer is the predominantly higher incidence among males as previously stated. It is also common knowledge that gastric acidity reaches unusually low levels during pregnancy and that remissions of peptic ulcer symptomatology occur during pregnancy (Strauss and Castle (5)). That some endocrine basis is present is not only suggested by clinical observations but by many experimental findings. Culmer, Atkinson, and Ivy (6) observed a marked diminution of the gastric secretions in response to anterior pituitary-like substances found in pregnant urine. Whether this hormone plays a direct part or whether it depends indirectly for its effect on the ovaries is not yet clear. Ferguson (7) has shown that progesterone does cause a marked diminution in the tonus and amplitude of contractions of isolated small muscle of the small intestine. Its effects on gastric mucosal activity, however, are varied (Manville and Munroe (8)). It may nevertheless bear some relationship to urogastrone previously discussed. All of these hormones are finely balanced and the upset of one unbalances the entire scale.

The part played by estrogen is still uncertain. Winkelstein (9) explored the subject quite intensively but his results were inconclusive. Ivy and his workers were unable to detect significant recession of peptic ulcer with estrogen therapy nor were the experimental results conclusive. Abrahamson and Hinton (2) studied the response of male patients possessing duodenal lesions to estrogen therapy. More than 80 per cent presented symptomatic cure and about 43 per cent roentgenologic cure, figures which are higher than in control groups. It is distinctive to note, however, that total and free acidity showed a tendency to increase rather than decrease as a result of estrogen therapy. Further work both clinically and experimentally is taking place with estrogens, testosterone, and anterior pituitary-like substances.

Again in gastric carcinoma the high incidence of the diseases in the male 3:1 suggests the endoerines as a factor. The relationship of estrogen to carcinoma, especially in the genital organs, has received special focus. Murlin (10) has demonstrated increased cellular activity in response to estrogens and androgens. Excessive excretions of cholesterol into the urine of carcinomatous individuals without increased nitrogen output suggests a change in steroid metabolism. In some experimental studies the production of carcinoma was accomplished only when theelin was added to a carcinogenic hydrocarbon. In contrast to these findings some workers report no carcinogenic stimulation by estrogen. It may be inferred that the balance of androgen, and some of the other steroids is of greater importance than the effect of each individual hormone.

Gastro-intestinal disease is yet a tremendous problem since the pathologic physiology and etiology are not yet well understood. In spite of the many advances in surgical techniques and pre- and postoperative care with reduction of mortality and morbidity rates, recurrence rates are still too high. Whether the relationship of the hormones to these diseases will provide a therapeutic way out still is far from settled. Much more experimental work is required and many complex problems have unbroken surfaces but the solution will be facilitated and hastened through experimental, physiologic surgery.

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## MENINGIOMA AT THE INTERNAL AUDITORY MEATUS

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The relative infrequent occurrence of meningiomas in the posterior fossa when compared to those found above the tentorium is apparent from the statistics published in "Meningiomas" by Cushing and Eisenhardt (1). Further subdivision of these tumors in the posterior fossa is made by the authors who split off a small group of which the outstanding characteristic is the resemblance it bears to the symptomatology of the acoustic tumors. In this group is one case history of a very small meningioma which previously had been described in detail by Monrad-Krohn (5). In the discussion of this case Dr. Cushing points out the extreme rarity of such lesion, he lists the other few similar cases reported and cites a solitary case encountered by Dandy in a very large experience with operations on the trigeminal and acoustic nerves in the lateral recess. Since the publication of "Meningiomas" in 1938, Gardner and Turner (3) reported a meningioma 1.5 cm. in diameter arising from the dura in the region of the porus and adjacent to but separated from a Schwannoma in the angle. A reference to two cases is made by Lysholm (4) in a paper on the X-ray diagnosis of recess meningiomas. Scott (6) describes a meningioma within the internal auditory canal encountered in some studies he was making of sections of the petrous bone. The rarity of these lesions and the resemblance in many details to the case of Monrad-Krohn had led to the reporting of the following case.

### CASE REPORT

*History* (Adm. 485487). S. T., a 45 year old unmarried woman, was sent into the hospital by Dr. Lester Coleman with a diagnosis of acoustic tumor. Following an upper respiratory infection some four years previously there had been a sudden onset of tinnitus in the left ear. So sudden was the appearance of this symptom that the patient was first aware of it on using the telephone, and registered a complaint with the telephone company that the instrument was out of order. The tinnitus persisted, and loss of hearing in the left ear gradually advanced to the stage of almost complete deafness. During this four year period there were occasions when the patient walked somewhat unsteadily and suffered from vertigo. Two weeks prior to admission to the hospital she first noted a slight twitching of the left lower eyelid. The twitching lasted only a short time but recurred at frequent intervals, and subsequently spread to involve the cheek and the upper lip. In the intervals between twitchings the face felt stiff. At no time had there been any severe headache nor any other complaints referable to the nervous system.

*Examination:* The patient sometimes postured the head with the occiput to the left. There was an occasional nystagmoid jerk on looking to the right. There was bilateral corneal hypesthesia and questionable slight hypalgesia of the first branch of the left fifth nerve. The left palpebral fissure was wider than the right and there was a slight weakness of the muscles innervated by the left seventh nerve, peripheral in type. Hearing was practically absent and vestibular responses were absent on the left side. Taste seemed normal. In the lower extremities the deep reflexes were a shade more active on the left than on the right side. No other abnormalities of the central nervous system were noted.

X-ray examination of the petrous bone was first reported as showing an erosion near its

tip. Studies made of the films subsequent to the operation were reported as showing slight but distinct increase in density on the left side posterior to the petrous apex in the region of the porous acousticus.

*Course:* On February 27, 1942 a hemi-suboccipital craniotomy was carried out under local anesthesia with the patient in the sitting position. When the cerebellum was retracted a cherry-sized tumor springing from the lateral dura was uncovered. Its mesial surface was quite free from the pons. The tumor was irregular in shape and had a nodular surface. Its gross appearance was that of a meningioma rather than that of the usual acoustic tumor. At first neither the seventh nor the eighth nerves could be seen. But as bits of the tumor were removed with a curette the nerves were brought into view. The seventh nerve was stretched across the antero-superior surface and the eighth nerve at the antero-inferior surface of the growth. When the tumor had been removed these nerves were visualized entering the porus, but they were separated by an appreciable space, giving the appearance, as noted by one observer at the operation, of a wishbone. The tumor appeared to spring from the posterior lip of the porous acousticus. It was reported to be a meningioma.

The postoperative course was entirely uneventful. The tinnitus disappeared promptly, but there was no improvement in hearing. Taste was lost over the anterior two-thirds of the tongue on the left side.

The patient was seen eleven months after the operation. She complained again of tinnitus. Hearing was completely absent on the operated side, and the patient believed that it was somewhat diminished on the other side. She stated that at times the left side of her face felt stiff, and that when she is very tired there is an occasional twitch of the left lower eyelid. On examination there appeared to be a slight weakness of the left side of the face. Hearing was absent on the left. Taste was lost over the anterior two-thirds of the tongue on the left. No loss of sensation of the face or canal of the ear could be found.

*Comment:* The loss of taste which followed the operation can be explained by injury to the nerve of Wrisberg. This is readily understood when the position of the tumor is recalled. In its growth it separated the seventh and eighth nerves. Undoubtedly the nerve of Wrisberg which was not seen at the time of the operation was injured during the removal of the tumor. It is not so easy to explain the absence of interference with taste prior to the operation. In this connection the exceptionally fine article by Furlow on *Tic Douloureux* of the Nervus Intermedius (2) is recalled.

#### SUMMARY

A case of a small meningioma in the cerebello-pontine angle is described. It is of interest, not only because of its comparative rarity, but because of the abrupt onset of the eighth nerve symptoms, the irritative phenomena of the seventh nerve and the operative trauma to the nervus intermedius.

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## THE RELATIONSHIP OF ESTROGENS TO DYSURIA AND INCONTINENCE IN POST-MENOPAUSAL WOMEN

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During the course of our studies of various aspects of the menopause, we were impressed with the frequency with which post-menopausal women complained of some disorder of micturition, such as frequency, urgency, dysuria or urinary incontinence. Our attention was also drawn to the fact that very frequently cystoceles or rectoceles or uterine prolapse would become first noticeable to the patient after the menopause. It seemed to us that there might be some relationship between the occurrence of these symptoms and the development of a deficiency of estrogenic hormone. Accordingly, about seven years ago we began a series of studies designed to determine whether there was any relationship between these symptoms and estrogen deficiency. In an earlier publication we reported our observations in 16 cases (1). Here we wish to report the results of our studies in an additional 20 cases.

### METHODS AND MATERIALS

Of the 20 cases studied 12 complained of dysuria and frequency and 8 of incontinence on coughing, laughing or sneezing. The ages varied from 49 to 71 years. Of the 20 patients, 15 were multipara; 3, primipara and 2, nullipara. Five had had some form of vaginal plastic (1, a parametrial fixation for prolapse and a vulvectomy for kraurosis; 2, anterior colporrhaphies for cystocele and 2, urethroplasties for urinary incontinence). Ten patients had moderate cystourethroceles; 4 of these complained of incontinence.

All patients were submitted to the routine general medical and gynecologic examination in addition to cystoscopy. During the past three years cystometric determinations were also performed. The estrogen status of the patient was determined by the means of vaginal smears. The smears were prepared according to the aqueous fuchsin technique which we have employed routinely for the past seven years (2, 3).

In none of the 20 cases could we find any evidence of infection in the urinary tract. In 17 of the cases cystoscopic examination revealed slight congestion of the trigone. The usual treatment of these cases with bladder irrigations, silver nitrate instillations, etc., resulted in only temporary relief of the frequency and dysuria but had no effect on the incontinence. All of the 20 cases manifested varying degrees of estrogen deficiency.

In order to determine whether the estrogen deficiency was etiologically related to the urinary tract symptoms these patients were given estrogen therapy for periods varying from 4 to 12 weeks. After the institution of estrogen therapy vaginal smears were taken twice weekly and cystometric determinations performed when the vaginal smears showed a full estrogenic effect. The results of our cystometric studies are being reported elsewhere.

*Dosage of estrogens.* Twelve of the patients were given estradiol benzoate (Progyon B) in doses of 10,000 R.U. three times weekly. Eight of the patients were given estradiol dipropionate (Diovoeylin) in doses of 1 mg. three times weekly or 2.5 mg. twice weekly.

*Effect of estrogens on frequency and dysuria.* Of the 12 cases treated, 10 reported considerable improvement at the end of two weeks. Six patients were completely relieved at the end of three weeks. At the end of four weeks all but 2 reported complete relief. Of the 2 remaining cases, 1 remained unimproved and 1 reported aggravation of the symptoms. Relief of symptoms was paralleled by evidence of progressive estrogenic effects in the vaginal smears. Patients remained symptom-free for periods varying from 3 to 17 weeks after discontinuation of the estrogens. Recurrence of symptoms was found to be associated with reappearance of signs of estrogen deficiency in the vaginal smears.

*Effect of estrogens on urinary incontinence.* Of the 8 cases complaining of urinary incontinence, 3 were completely relieved at the end of approximately three weeks of therapy (one case was given 20,000 R.U. estradiol benzoate three times weekly; two cases, 5 mg. estradiol dipropionate twice weekly). The 5 cases receiving the smaller doses (4,000 R.U. estradiol benzoate or 1 mg. estradiol dipropionate three times weekly) were either only slightly or not at all improved after three weeks of therapy. The dose of estrogens was then increased in these cases to 20,000 R.U. estradiol benzoate three times weekly or 5 mg. estradiol dipropionate twice weekly. Following two weeks of therapy with the increased dosage, the incontinence was relieved in three of the patients. Two remained unimproved. The duration of the therapeutic effect varied from 4 to 6 weeks after the discontinuation of the estrogens. The incontinence promptly responded thereafter to additional estrogen therapy.

*Correlation of vaginal smear findings and symptoms.* The vaginal smears which were taken twice weekly revealed progressive estrogenic effects which paralleled, with but slight deviation, the clinical picture. Thus in the group of patients treated with high doses of estrogens in whom clinical improvement was steady and rapid, the smears showed good estrogenic response at the end of a week and full estrogenic reaction at the end of the second week, a full week before the maximal therapeutic effect was observed. In the group of cases treated with small doses of estrogens the inadequacy of the dosage was attested by the incomplete estrogenic effects in the smears as well as by the failure to appreciably influence the symptoms.

It is noteworthy that when the same patients were subsequently treated with much larger doses of estrogens the striking clinical improvement was paralleled by the appearance of marked estrogenic effects in the smears. Furthermore, when symptoms gradually returned after the discontinuation of estrogen therapy, the vaginal smears were found to have regressed to a state of deficiency comparable to that which existed before the institution of the estrogen therapy.

Four of the cases (2 complaining of frequency and dysuria and 2 of incontinence) were not improved in spite of intensive estrogen therapy and evidence of full estrogenic effect in the vaginal smears. The failure of these cases to respond

to estrogens may be attributable to the fact that these patients probably had extensive anatomic defects in the sphincter mechanism. Three had cystourethroceles, one had had a parametrial fixation operation for prolapse and had developed the incontinence thereafter.

It is evident that the incontinence in a given case may be contributed to by two independent etiologic factors, viz: an anatomic lesion and an estrogen deficiency. Correction of one factor (e.g., the estrogen deficiency) may not be sufficient to restore complete functional efficiency to the sphincter mechanism.

*Control studies with progesterone, testosterone and saline.* In order to determine whether the therapeutic effect observed after the estrogenic injections was specific and also as a psychotherapy control a number of the women, when symptoms recurred, were given progesterone, testosterone or saline. Five women were given injections of progesterone (10 mg. three times weekly for three weeks); 9, testosterone propionate (25 mg. three times weekly for four weeks); and 6 were given subcutaneous injections of saline three times weekly.

*Comparative therapeutic results obtained with progesterone, testosterone and saline:* Of the 5 patients treated with progesterone, 1 reported slight improvement at the end of two weeks and 4 no improvement. Of the 9 cases treated with testosterone, 5 reported no improvement, 2, slight improvement and 2, aggravation of symptoms. Of the 6 patients treated with saline, 1 reported very slight improvement of the frequency, of the remaining 5, 4 reported no improvement and 1 reported aggravation of the symptoms.

The slight improvement which a few of the patients reported after the progesterone and saline injections are obviously to be interpreted as psychotherapeutic effects. The same is probably true of the response of the 2 cases to testosterone. There is however, some experimental evidence which indicates that testosterone may have an estromimetic action (4) although the dosage in these cases was too small to produce demonstrable estrogenic effects in the smears.

#### DISCUSSION

On the basis of these observations it seems permissible to conclude that an estrogen deficiency in elderly women may be the cause of frequency, dysuria and even incontinence. The estrogen deficiency *per se*, however, does not invariably cause the urinary incontinence, since in many instances we have found evidence of marked estrogen deficiency without this disorder.

As regards the incontinence, there appear to be two etiologic factors, viz., 1) the long standing estrogen deficiency and 2) some anatomic defect in the sphincter mechanism, the latter being the result of an old obstetric injury. When the patient is adequately supplied with estrogens by her functioning ovaries, this sphincter defect may not be sufficiently marked to interfere with functional efficiency, but following a long period of estrogen deprivation, with its attendant atrophy and loss of tone in the contiguous supporting tissues, the functional efficiency of the sphincter may become impaired to such a degree that incontinence results. This theory would satisfactorily explain why women frequently do not develop incontinence until after the menopause.

Perhaps the chief practical value of this study consists of the demonstration that some cases of urinary incontinence can be relieved by estrogens and do not require surgical treatment. On the basis of our observations we now submit all elderly women complaining of urinary incontinence to an investigation of their estrogen status. If they are found to be markedly deficient in estrogens they are given an intensive course of estrogen therapy. Not infrequently, these patients are so improved that operation is unnecessary. In those cases, however, in which there is a cystocele or uterine prolapse an appropriate vaginal plastic operation can be performed after the estrogen therapy. Histologic studies of the musculo-fascial tissues of the vagina before and after estrogen therapy indicate that the estrogens markedly increase the vascularity and thickness of these tissues facilitating the dissection and the anatomical restitution. Furthermore, because of the improved blood supply, the estrogens probably promote more satisfactory healing.

#### CONCLUSIONS

1. Long standing estrogen deficiency may cause dysuria, frequency, urgency and urinary incontinence in post-menopausal women.
2. Intensive parenteral therapy with estrogens relieves the symptoms in the majority of instances at the end of three or four weeks.
3. Vaginal smear control is essential to insure adequacy of estrogen therapy.
4. It is recommended that post-menopausal women complaining of incontinence be given a therapeutic trial with estrogens before resorting to surgical procedures.

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## EXTRATESTICULAR CHORIOEPITHELIOMA IN A MALE PROBABLY PRIMARY IN THE URINARY BLADDER

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Although chorioepithelioma is well known to gynecologists, it is rarely encountered in the male. On occasions chorioepithelioma is seen in testicular neoplasms. It is however an extreme rarity to find this condition in the male where the primary focus is proven to be extratesticular. In order to be certain that the tumor was not primary in the testes, serial sections of both testicles must be studied grossly and microscopically not only to exclude a small area of chorioepithelioma, but it is also necessary to be certain that there is no evidence of a healed scar in the testis which may have been the primary focus. There are only ten\* such cases in the literature at the present time (1-10). We wish to add an eleventh case to the series. It is of interest that this represents the fourth case from this hospital and the third case in which the bladder was probably the primary focus.

### CASE REPORT

*History:* (Adm. 499616). A. M., a white man 57 years of age was admitted to The Mount Sinai Hospital December 27, 1942. He gave a history of intermittent gross hematuria for several months. Four weeks prior to his admission he had a rather profuse hematuria. He was taken to another institution where intravenous urography was done and showed a normal upper urinary tract, but there was a filling defect on the left side of the bladder in the cystogram shadow. Cystoscopy was carried out at that time and the patient was told that he had a calculus of the bladder and required operation. A suprapubic cystotomy was done and the surgeon encountered an extensive neoplasm of the bladder which bled very freely. Biopsy specimens were taken and the growth was fulgurated. The biopsy specimens were reported as "carcinoma." Since the family was advised that the condition was inoperable, the patient was transferred to our care with a suprapubic drainage tube in place. Since operation the urinary drainage had been brownish and bloody from time to time. He had had episodes of severe singultus. His anemia had been treated with repeated transfusions.

*Examination:* The patient was a pale, chronically ill man with some cough and mild dyspnea. The breasts were hypertrophied and firm. The heart appeared normal and the lungs were clear except for slight dullness over the right upper lobe. The abdomen was normal except for the recent suprapubic scar with a draining suprapubic tube. There was a vague sense of a mass in the region of the wound. The testes on palpation were normal. There was no abnormality on rectal examination.

*Laboratory data:* The urine was grossly cloudy and brownish in color and microscopically showed many pus cells and red blood cells. Blood urea nitrogen was 10 mg. per cent. Studies of the blood phosphatase were reported as showing an acid phosphatase of 12 and an alkaline phosphatase of 9 King Armstrong units. Excretory urography revealed a grossly normal upper urinary tract on both sides. The cystogram shadow, however, showed many filling defects in the wall of the bladder which were interpreted as neoplastic involvement. Roentgenogram of the chest on admission disclosed a metastatic tumor in the

\* Report of Hoelzer (11) could not be obtained.

right upper lobe about two inches in diameter and a second rounded shadow at the level of the eighth rib on the right side.

*Course:* It was obvious that the operation of total cystectomy which had been considered for this patient was out of the question in view of the metastases to the lungs. In an effort to check on the reported pathology of the tumor, the slide from the other institution was submitted to both Drs. Klemperer and Otani. Their diagnosis was chorioepithelioma and was based upon the findings of hemorrhage and cell structures similar to Langhans cells and syncytial masses. Additional biopsies were taken by us cystoscopically from the tumor and these were likewise reported as "fragments of partially necrotic chorioepithelioma."

In view of this diagnosis, the question of therapy arose. Although we felt that we were dealing with a case of primary chorioepithelioma of the bladder, we were not certain that the testes might not be a primary focus. In addition to this, Huggins had stated to the senior author that bilateral orchiectomy might be done in cases of carcinoma of the prostate, carcinoma of the male breast and chorioepithelioma. Accordingly, bilateral orchiectomy was done. Serial sections of both testes failed to show any abnormality, either tumor or scarring. A Friedman pregnancy test done on the patient's urine was reported as "strongly positive."

The patient's course during his stay in the hospital was progressively downhill. He became more anemic and was troubled with intractable hiccough. A right phrenicectomy was done which relieved this condition. X-ray therapy was given but had no beneficial effects. The patient became progressively worse and finally died March 16, 1943. It was most unfortunate that post-mortem examination was not permitted.

*Summary:* The outstanding clinical features were as follows: hemorrhagic necrotic and extensive tumor of the bladder; metastases to the lungs; positive pregnancy test on the urine; biopsies of the tumor showing chorioepithelioma; and absence of any lesion in the removed testes. On the basis of these findings we feel that this patient had a primary extratesticular chorioepithelioma, probably primary in the urinary bladder. No mention of hyperplasia of the Leydig cells was made. There was no evidence of gynecomastia.

#### DISCUSSION

Chorioma was first described by Volkmann (13) in 1867 as a destructive placental polyp. In 1895 Marchand (14) by a minute comparison of the tumor cells with fetal villi, concluded that this tumor arose from chorionic epithelium reproducing both syncytium and Langhans cells. Waldeyer (15) in 1868 observed polypoid tumor masses extending from a testicular teratoma into the pelvic veins which he compared with hydatid mole in the female. In 1878 Malassez and Monod (16), and later Carnot and Marie (17) described similar tumors of the testicle and noted the multinucleated giant cell masses which were in relation to the blood vessels and designated the growth "*sarcome angio-plastique*." In 1902 Schlagenhauser (18), Wlassow (19) and Steinert (20) all pointed out the exact resemblance of chorioma testis to chorioepithelioma of trophoblastic origin, traced the origin of the syncytial masses from epithelium of the testicular growth, identified glycogen holding Langhans cells and noted the hemorrhagic character of the metastases. Warthin (21), Cooke (22), Herzenberg (23) then reported cases of chorioepithelioma of the testis with hypertrophy of the breasts and the secretion of colostrum, thus adding features of pseudogestation. In 1930 Aschheim and Zondek (24) found the pregnancy test positive in men with chorioepithelioma.

Heaney (5) summarized the following theories of origin of chorioepithelioma of the testis.

1. Teratomatous. Often in the original tumor and occasionally in the metastases, teratogenous elements are found. Hornicke believes that the teratogenous elements are frequently overlooked.

2. Endothelial. Some of the French authors believe in this theory. They coined the term "*sarcome angioplastique*."

3. Epithelial genesis.

4. Totipotent cells. The incidence of chorioepithelioma of the testis in years of spermatogenic activity suggest the origin from totipotent cells.

5. Trauma, often a factor.

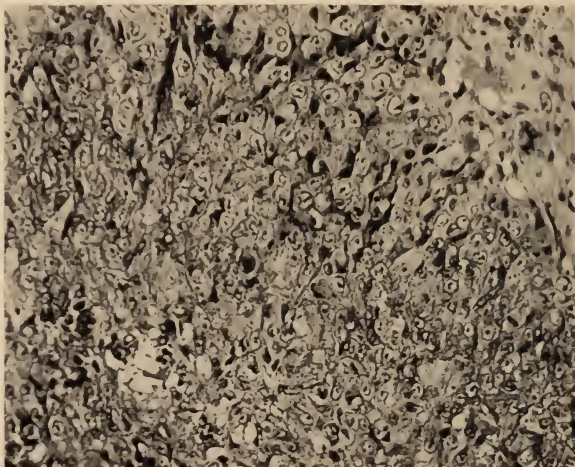


FIG. 1. Photomicrograph of bladder tumor showing Langhans cells and syncytium

6. Hypothesis of misplaced blastomeres with subsequent malignant degeneration.

7. The work of Hausmann and Budd (25) on unattached retroperitoneal tumors, chorioepithelioma in the male included, has revived the concept that extratesticular chorioepithelioma may originate from remnants of the embryonal urogenital apparatus. Weinberg (8) states that chorioepithelioma arising either retroperitoneally or within the mediastinum may be explained on the basis of germinal rests (the *plica urogenitale*), or in malignant transformations, as well as in unilateral development of teratomas.

Pollack (26) in reporting a case of malignant teratoma of the bladder discusses the origin from "dysontogenetic rests of the dorsal mesodermal segments which are carried down to the bladder anlage by the caudally growing Wolffian duct."

If this theory is correct, then chorioepithelioma of the bladder could arise from a unilateral development of a teratoma. Weinberg points out that in the cases reported in the literature, "the metastases from ectopic chorioepithelioma almost invariably showed no teratomatous elements, only chorioepithelioma." Kantrowitz (6) specifically notes that in large so-called primary ectopic chorioepitheliomata, the remnants of teratomatous elements may be so few and so well localized as to defy their discovery except by the examination of serial sections through the entire tumor.

#### ECTOPIC CHORIOEPITHELIOMA IN THE MALE

With very few exceptions, chorioepithelioma in the male arises in the testis. It is a highly malignant growth and the prognosis is very grave. Few cases have lived over two years. Extratesticular chorioepithelioma in the male is extremely rare. Prym (27) in a review of the literature of alleged cases of extragenital chorioepithelioma accepts only the case of James Ritchie (28). Ewing (12) suggests that these extragenital tumors are probably primary carcinoma simulating chorioepithelioma or are a metastasis from chorioepithelioma of the testis where the primary lesion is overlooked. Nevertheless, Heaney in addition to reporting a case of extragenital chorioepithelioma in a man, accepts the cases of Ritchie, Bonney, Parkes-Weber, Miller and Browne, Krassnianskaya, Lambert and Knox.

Kantrowitz however did not feel that all those cases should be accepted because there was no evidence that the testicles were sufficiently carefully examined both grossly and microscopically in some of the above reports. Up to the time of this writing the following cases of extratesticular chorioepithelioma in the male can be accepted.

1. Miller and Browne (1): 39 year old man with the primary tumor mass behind the liver. The testes were normal.

2. Krassnianskaya (2): 72 year old man with the primary tumor in the hilum of the left lung. Serial sections of both testes were normal.

3. Arendt (4): 20 year old male with a mediastinal teratoma and chorioepithelioma. Gynecomastia was present. The testes were atrophic with atrophy of the tubules and marked proliferation of the Leydig cells. Biological tests were not done.

4. Heaney (5): 40 year old man with a retroperitoneal mass pushing forward the stomach and pancreas. The pathological diagnosis was primary retroperitoneal chorioepithelioma probably derived from the urogenital anlage. There was no abnormality in the testes, the right was atrophic. No teratomatous elements were found.

5. Kantrowitz (6) (from The Mount Sinai Hospital): 22 year old man with dyspnea, orthopnea, bloody expectoration and loss of weight. The breasts were not enlarged. Post-mortem examination showed a primary teratoma of the anterior mediastinum with chorioepithelioma. The tumor invaded the superior mediastinum and both lungs were studded with metastases. There were no metastases elsewhere on careful gross and microscopic examination. The

Aschheim-Zondek test was positive using 1.5 to 2.4 cc. of urine. Ether extracts of the lung metastases for female sex hormone (Frank) were negative for 20 grams of tissue but the alcohol extract for anterior pituitary hormone with 1 cc. equal to 9.5 grams of tumor tissue gave positive results. Both testes were cut in 2 mm. thicknesses and were imbedded and sectioned. No tumor nodules or scars were found. There was hyperplasia of the Leydig cells.

6. Gerber (7) (from The Mount Sinai Hospital): 23 year old male with right flank, chest pain and blood tinged expectoration. There was a mass in the right lower abdomen, edema of the right lower extremity and multiple pulmonary metastases. Necropsy showed a grapefruit sized mass retroperitoneally over the right iliopsoas muscle which had invaded and obstructed the right ureter and right common iliac vein. There was necrosis and hemorrhage in the tumor. Multiple metastases were present in the lungs, liver, spleen and kidneys. The Aschheim-Zondek test was positive. The tumor was a chorioepithelioma. No teratomatous elements were found. Histologic studies of the testes, prostate, seminal vesicles and vasae showed no changes. There was no hyperplasia of the Leydig cells.

7. Weinberg (8) (from The Mount Sinai Hospital): 70 year old man with urinary difficulty and gross hematuria including clots. He also had blood streaked sputum. Blood urea nitrogen was 28 mg. per cent. Shortly after admission the patient went into heart failure and died before further urologic studies could be carried out. Necropsy showed no evidence of gynecomastia. There was a tumor of the bladder 7 x 8.5 cm. involving the right half of the trigone, right and posterior walls of the bladder. Microscopically this tumor showed the characteristics of chorioepithelioma. There were generalized metastases in almost all the organs of the body. The testes were examined by serial block sections and showed no microscopic evidence of chorioepithelioma. Spermatogenesis was active. Nodular areas of interstitial cell hyperplasia were present. The rat test for gonadotropic hormone gave a positive reaction with 0.1 cc. of urine which is equivalent to 10,000 rat units per liter. The rabbit test gave a strong reaction. Test for estrogenic hormones was negative. Extracts of the lung metastases failed to show either gonadotropic or estrogenic hormones.

8. Mathieu and Robertson (9): 27 year old male with epigastric pain, nausea and vomiting and history of hemoptysis. A mass was palpable below the left costal margin. X-ray examination showed a metastasis to the lung and barium meal showed displacement of the stomach by a mass. Mild gynecomastia was noted. Necropsy showed a large retroperitoneal tumor displacing the pancreas and stomach. Hemorrhagic metastases were present. The microscopic diagnosis was chorioepithelioma. After fixation, each epididymis and testis was sectioned at close intervals. No tumors, scars or gross abnormalities were noted. Microscopically no tumor cells were found in the testes. Spermatogenesis was active and hyperplasia of the Leydig cells was noted.

9. Erdmann, Brown and Shaw (10): 45 year old man with left lumbar pain, hematuria and pyuria. Mass felt in left flank. Laparotomy showed inoperable vascular tumor behind left kidney. Aschheim-Zondek test on urine was negative.

Post-mortem examination showed chorioepithelioma of left lumbar mass and lung metastases. Both testes were sectioned in 2 mm. blocks and one section was examined from each block. There was no evidence of tumor or scarring. The authors also quote Staemmler's report of the finding of testicular tissue at the root of the mesentery in 2 cases of 13 control autopsies.

These authors are extremely rigid in their acceptance of reports of extragenital chorioepithelioma in the male. They tabulate the following cases in the literature of this condition with the year of publication, results of testicular examination, gynecomastia and results of pregnancy tests. (Bostrom 1902, Ritchie 1903, Askanay 1906, Frank 1906, Bonney 1907, Fischer 1908, Nakayama 1910, Weber 1918, Lambert and Knox 1920, Miller and Browne 1922, Krassnianskaya 1929, Shultze 1930, Fenster 1931, Arendt 1931, Heaney 1933, Kantrowitz 1934, Ellis 1934, Gerber 1935, Symoendis 1935, Jaquenod 1936, Carver and Stewart 1936, Mathieu 1939, Weinberg 1940). Of all the above reports they will only accept the reports of Kantrowitz, Gerber, Fenster and Weinberg. The reasons for the rejection of the other cases was because the reports indicated either areas of testicular atrophy or the failure to take careful serial sections of both testes. There are several reports in the literature in which a minute area of atrophy or pathology is present in a testicle. The case of Carver and Stewart (42) is very much in point in that it showed within the testicle one cyst 3 mm. in diameter and another 1 mm. diameter area of mucinous tissue. We cannot understand why the first case of Mathieu and Robertson (9) was not accepted since it fulfilled all the criteria of a primary extragenital chorioepithelioma in the male.

10. Fenster (3): Quoted by Erdmann (10).

11. Hyman and Leiter: Reported above.

It is remarkable that four out of the above eleven cases of ectopic chorioepithelioma in the male should have occurred and been studied at The Mount Sinai Hospital. In all four cases the biologic tests for gonadotropic hormone were positive.

Before concluding, one must say a few words about chorioepithelioma of the bladder. Although Weinberg found reports of five cases of so-called primary chorioepithelioma of the bladder, he could only accept the case of Djewitzki (43). This was a 75 year old virgin female with dysuria and hematuria. Careful autopsy showed a tumor of the posterior wall of the bladder and multiple metastases. Both the bladder tumor and metastases had the typical appearance of Marchand's chorioepithelioma. Weinberg's case is undoubtedly a primary chorioepithelioma of the urinary bladder. Although our case showed chorioepithelioma in an extensive neoplasm of the bladder, the fact that post-mortem examination was not done makes one say that our case is probably one of primary chorioepithelioma of the bladder in a male.

#### SUMMARY

1. A case of extensive bladder tumor in a male with a positive biopsy of chorioepithelioma was reported.

2. The outstanding clinical features in this case were dysuria, frequency of

urination, gross hematuria, pulmonary metastases and the presence of large amounts of gonadotropic hormone in the urine. Gynecomastia was present.

3. Bilateral orchidectomy and roentgen-ray therapy had no beneficial effect on the tumor.

4. Serial microscopic sections of both testicles failed to reveal any abnormality, scars or primary focus in the testes.

5. This case represents the eleventh true extratesticular chorioepithelioma in a male according to the rigid criteria for this diagnosis, and the third case of primary chorioepithelioma of the urinary bladder.

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## RETROPERITONEAL ABSCESS AND PHLEGMON

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It is fitting to present this subject as a tribute to Hiram N. Vineberg because he was a pioneer in the surgery of pelvic suppuration. In a period which was characterized by uncertainties and vacillation in the management of suppuration derived from the pelvic organs he made significant contributions by his operative management of these cases. Among the difficult problems which he encountered was that of retroperitoneal suppuration derived from the pelvic organs. Today the problem of retroperitoneal suppuration, whether derived from the pelvis or from other sources, remains a difficult one. It is a privilege to attempt here a contribution toward its solution.

Acute retroperitoneal infections derived from a variety of sources have long been known to be grave lesions which at times present great difficulties both in diagnosis and in treatment. This statement appears to apply with equal force whether the infection arises from the pelvis or from other regions. Despite the clinical importance of the subject, and the fact that retroperitoneal infections cannot be classified among the rarities, the literature is composed essentially of reports dealing with individual cases. Such reported cases are related to particular regions or special sources of infection. Thus in the Edwin Beer commemorative volume of the *Journal of The Mount Sinai Hospital* I called attention to an obscure variety of retroperitoneal infection\*. Others have made similar contributions. However, the subject as a whole has not as yet received the comprehensive consideration which its importance warrants. Dr. E. E. Arnheim and I have gathered 65 cases from the records of The Mount Sinai Hospital in the period from 1925 to 1942, cases from our own as well as from other surgical (and also medical) services. We propose to base a thorough study of the retroperitoneal infections on an analysis of these cases. Here I shall submit a general outline of the subject, with special reference to clinical classification, the diagnosis of the less obvious varieties, and the principles of operative treatment. Since the group of cases of pelvic origin comprises a relatively small proportion of the whole number of cases, and since the pelvic cases do not appear to pose different problems from the others, undue emphasis will not be placed on that group. However, the particular purpose of this presentation warrants the detailed description of at least one case of retroperitoneal infection of pelvic origin. This will be set forth, especially because a recent reoperation in this case has provided a unique opportunity to gain some idea of the pathogenesis of the retroperitoneal infection.

The anatomy of the retroperitoneal space will not be here reviewed. However, even its cursory consideration will lead to the conclusion that the limit

\* Neuhoef, H.: Retroperitoneal Abscess with Obscure Clinical Manifestations. *J. Mount Sinai Hosp.*, 4: 843, 1938.

of the space cannot be too sharply defined. Thus at its upper limits the space is continuous with the extraperitoneal subphrenic space. Below are the extraperitoneal spaces related to the rectum, bladder, prostate, and female pelvic organs. In this presentation infections localized to the upper or lower limits of the space will be omitted from consideration not only because they can be more properly regarded as extraperitoneal rather than retroperitoneal but also because their clinical features and the problems which they raise are different from those of infections in the main retroperitoneal space.

An analysis of the 65 cases to which reference has been made led to their simple grouping on the basis of combined clinical, anatomical, and pathological aspects. There was overlapping in some instances but in the main the cases fell with surprising readiness into two main groups. The classification is of clinical usefulness; however it appears to be of special value in the decision as to the type of operative approach in the individual case. The classification is as follows:

A. Localized form: Abscess

1. Lumbar
2. Iliac
3. Subphrenic only (omitted from consideration)
4. Pelvic only (omitted from consideration)

B. Diffuse form: Phlegmon

1. Lumbar
2. Iliac

#### LUMBAR RETROPERITONEAL ABSCESS

The lumbar portion of the retroperitoneum (retroperitoneal space) extends from the twelfth dorsal vertebra and twelfth rib to the promontory of the sacrum mesially and the iliac crest laterally. The surgical significance of the fact that the floor of the space is formed not only by the quadratus lumborum but also by the psoas muscle will be stressed. The fascia covering these muscles is for the most part well developed and firmly anchored at the limits of the lumbar retroperitoneal space. It is this membrane which tends to confine retroperitoneal abscesses to that space and thus render difficult their early recognition and surgical management. The relationship of the kidney to the retroperitoneal space is of special interest because a proportion of the cases of lumbar retroperitoneal abscess is of renal origin. However it would lead too far afield to describe the fascial connections. Suffice it to say that under exceptional circumstances suppuration derived from the kidney can extend into the retroperitoneal space instead of producing the customary perinephric abscess.

The lumbar retroperitoneal space may be infected by direct extension from suppuration in an adjacent organ (kidney, colon, appendix, spine), by lymphatics and lymph nodes, or apparently by metastasis. However, the source remained unknown or undetermined in 9 of our 25 cases. Trauma preceded the onset of symptoms in 2 of these 9 cases, and appears to play a definite role in causation just as in the iliac group to be discussed. The situation of the abscess in the lumbar retroperitoneal space varied, perhaps in keeping with the pathogenesis.

Abscesses lay either underneath the lumbar aponeurosis of the transversalis muscle or were immediately retroperitoneal, pushing the peritoneum forward. In one instance, however, the abscess was located chiefly within the psoas muscle.

The bacteriology is definitely related to the etiology. Thus in the case of metastatic abscess secondary to furuncles of the skin the organism was staphylococcus aureus. Most of the abscesses of renal origin contained either the staphylococcus aureus or the bacillus coli. Abscesses secondary to acute pharyngitis or upper respiratory infection cultured the streptococcus hemolyticus. Bacillus coli and the enterococcus were grown from abscesses of appendiceal origin. It is perhaps significant that cultures from the abscesses of unknown origin grew either streptococci of staphylococci, suggesting that they too may be metastatic.

The clinical manifestations of the lumbar retroperitoneal abscess may be grouped into general and local. The local features tend to be more obvious than those of the pelvic variety of retroperitoneal abscess. Nevertheless they are at times quite obscure for considerable periods. Therefore emphasis should be placed on the necessity for seeking diagnostic leads in the early phase of the infection. Although stress will be placed anew in the consideration of iliac retroperitoneal abscess on the value of an examination under anesthesia for a suspected mass in cases in which muscle spasticity exists and apparently interferes with the palpation of a mass, the point applies with about equal force to lumbar retroperitoneal abscess.

Concerning the clinical manifestations there was a history of pain and fever in all cases. Since the age range was from 10 months to 75 years it is obvious that in some cases pain could only be assumed to exist. Pain was at times too diffuse to be regarded as a local sign. In most instances however it had some localizing value. Most often pain was in the lumbar region, but occasionally in the hip, thigh, or abdomen. The wide range in clinical manifestations becomes obvious when it is realized that the duration of symptoms before hospital admission ranged from 4 days to 9 weeks.

On physical examination there was tenderness in and spasm of the lumbar musculature on the affected side in almost all cases. The important point to be made is that a tender mass (either in the lumbar region or in the abdomen) was felt only in little more than half the cases. It was this absence of a mass which led to protracted observation during lengthy periods in which septic or toxic states often continued and the areas of suppuration enlarged considerably. In cases in which abdominal masses were present they were of substantial proportions and located in or at the lower hypochondrium. Psoas (hip) spasm is not a feature of the lumbar variety of retroperitoneal abscess yet was present in 5 of the 25 patients. Its presence in these cases can be assumed to be due to extension of the abscess from the lumbar region mesially over the psoas muscle.

From the foregoing it becomes evident that the diagnostic criteria of lumbar retroperitoneal abscess are not precise and that the nature of the lesion is apt to be unrecognized in its earlier phases. In this series of cases the lesion often was not suspected on admission to the Hospital. This is shown by the period:

of preoperative study and observation which extended up to one month from the time of admission (average period, 10 days). In some instances the diagnosis was not clear even at the time of operation, which was performed for suspected malignancy and not for abscess in several instances. Perhaps the most common error was to confuse the lesion with perinephric abscess in cases in which the retroperitoneal abscess was found at operation to bear no relationship to the kidney.

The operative approach to the extraperitoneal lumbar abscess should of course be extraperitoneal yet in 4 of the 25 cases in this series the peritoneal cavity was traversed for drainage because the diagnosis had not been established before operation. Of the two deaths in this series one was due to peritonitis following transperitoneal drainage. Difficulties in management, complications and the likelihood of secondary operations, can also be visualized as the sequelae of transperitoneal drainage. Thus emphasis should be placed upon a final examination under anesthesia just before a laparotomy for an abscess or an inflammatory mass whose location in relationship to the posterior peritoneal space is doubtful. Indeed it can be said that very little is lost by making an exploratory retroperitoneal incision even if found to be negative and hence followed by laparotomy. In fact the lumbar incision can be used with advantage for efficient drainage in *intrapertitoneal* abscesses situated at the posterior parietal peritoneum, as I, like others, have found to be the case upon a number of occasions.

The operative incision to be employed for a lumbar retroperitoneal abscess is one which can be termed the anterior half or more of the customary incision for exposure of the kidney. Special care should be taken to avoid the damaging effect of injury to the twelfth thoracic nerve. The situation of the incision must be placed in relationship to the mass and thus vary in accordance with the relationship of the mass to the kidney zone. At times the mass is not only indefinitely felt but also more mesially situated than is usually the case. Under these circumstances the incision is more in the nature of an exploratory one being deepened to peritoneum. The latter then is stripped away and retracted toward the midline as the exposure is deepened in order to approach the mass.

Once the peritoneum is visualized the danger of traversing it should have passed. The relationship of peritoneum to the abscess must always be defined before the abscess is entered otherwise the possibility exists that the peritoneal space will be entered during the enlargement of the opening into the abscess. The latter usually is of substantial proportions and thus requires liberal drainage. It also often is multilocular, especially in advanced lesions, and thus requires opening of the various loculations. In other words the type of operation which terminates with the introduction of a drainage tube as soon as pus is encountered is apt to be followed by both untoward complications and sequelae. The abscess should be adequately split open and unroofed, its contents evacuated, retractors inserted and all recesses fully visualized and laid open when necessary. With the knowledge that there are no pockets left behind all recesses and the main cavity can be snugly packed with gauze with the assurance that there will be no retention of pus. Tube drainage should be reserved for those exceptional

instances in which adequate unroofing of the abscess would damage important structures.

#### ILIAC RETROPERITONEAL ABSCESS

In this retroperitoneal region certain surgical anatomical features are of importance not only for operative treatment but also for diagnosis. The psoas and iliacus muscles are separated from the retroperitoneal cellular tissues by a thick (iliac) fascial membrane. The latter is attached laterally to the iliac crest, mesially to the brim of the true pelvis along the iliopectineal line. Below, the iliac fascia fuses with the transversalis fascia at its firm attachment to Poupart's ligament lateral to the external iliac artery. At the external iliac artery and vein the iliac fascia passes behind and the transversalis fascia in front of the vessels. Thus the iliac and transversalis fasciae comprise the sheath for the femoral vessels, and the pathway of infection from the upper thigh to the iliac fossa becomes evident. The structures within the iliac retroperitoneal space such as the ureter, the spermatic or the ovarian vessels can of course be direct sources of infection. However, the iliac lymph nodes in their three chains about the external iliac vessels are probably the most common source of iliac retroperitoneal abscess since they drain the inguinal lymph nodes, the external and internal genitalia, the prostate and the bladder. Indeed their zone of drainage is exceptionally wide including the lower abdominal wall up to the level of the umbilicus.

In our series there were 23 cases of iliac retroperitoneal abscess, almost the same number as lumbar retroperitoneal abscess. As in the latter group a substantial proportion (one-third) were of unknown or indeterminate origin, although not a few were due probably to iliac lymphadenitis. Known sources were the uterus and adnexa, the sigmoid, the appendix, the ureter, and extension of infection from the foot and thigh. Trauma (fall on the buttocks) was an assumed cause in a number of instances and since blood clots have been found in the abscess cavity at operation (infected hematoma), there can be no doubt as to its role.

The situation, size, and extent of iliac abscesses are related to their pathogenesis and the stage at which operation was performed. In some instances the abscesses were located within the substance of or in close contact with the psoas muscle. In cases of suppurative iliac lymphadenitis secondary to infection of the lower extremity the iliac abscess extended down to the inguinal (Poupart's) ligament. Retroperitoneal abscesses derived from the appendix were laterally situated. In one case the retroperitoneal suppuration was bilateral. The details of this extraordinary case, in which the infection followed a pelvic operation, will be set forth at the end of this section dealing with iliac retroperitoneal abscess.

The bacteriology parallels so closely that of lumbar retroperitoneal abscess that a statement of its features here would be largely a recapitulation.

Before a discussion of clinical manifestations reference should be made to the age factor in iliac retroperitoneal abscess. The age ranged from 7 months to

62 years, but the lesion was encountered in childhood with a disproportionate frequency. Thus four of the five cases of suppurative iliac lymphadenitis occurred among children. Contrasting with the lumbar variety of retroperitoneal suppuration the iliac type can be regarded as more distinctively an infection of childhood. In view of the frequency of psoas spasm in iliac abscess and of psoas (hip) spasm in tuberculous (and other) hip-joint infections in childhood the differentiation between these unrelated lesions becomes at times a problem of clinical importance. It is for that reason that attention is called here to the outstanding physical sign which is the same in both conditions.

Pain was a constant symptom being referred to the lower abdomen in about half the cases and to the lower extremity in the other half. In the latter instance pain was referred often to the hip, thigh, or knee. This was particularly true of those abscesses which involved the psoas muscle and presumably irritated branches of the lumbar plexus. Fever also was a constant accompaniment, chills occurring occasionally. The symptoms were of greatly varying duration before admission to the hospital from as short a period as 2 days to a protracted one of 5 months. In only one case, in which the retroperitoneal abscess was metastatic, was the blood culture positive (*streptococcus hemolyticus*) during hospital observation.

The clinical features varied during the hospital stay before operation. Inasmuch as suppuration was suspected at the outset in practically all cases and the preoperative period was not infrequently protracted (up to one month) it is obvious that the diagnosis often was obscure. Emphasis therefore should be placed on the few clinical features which offer criteria for the correct diagnosis. Direct tenderness in the iliac or inguinal zones or both was the most common sign. A definite or indefinite mass was noted in these regions in no more than half the cases and then usually only late in the evolution of the infection. Thus it is clear that the presence of an iliac mass should not be awaited for the diagnosis of an iliac retroperitoneal abscess. Similarly rectal tenderness, fulness, or mass was present in less than half the cases. The most striking sign was psoas spasm which was present in 11 of the 23 cases. Its absence in about half the cases is presumably ascribable to the fact that the abscess was more laterally disposed (away from the psoas and the mass of the iliacus) in these cases.

The difficulties in diagnosis become apparent when it is realized that in at least 3 of the cases of iliac retroperitoneal abscess in this series the incorrect diagnosis of acute appendicitis was made. Not a few of the lesions were found to be in an advanced state of suppuration, with commensurate difficulties at operation (and postoperative problems as well), at the time they came to operation. Therefore for this group particularly there appears to be ample justification for the advocacy of extraperitoneal exploration when the diagnosis of an iliac abscess is seriously entertained. As has been suggested for lumbar extraperitoneal abscess in cases in which a mass cannot be felt, examination under anesthesia may reveal a mass which could not be felt through the spastic lower abdominal wall. Even in the absence of a mass such signs as a tender fulness by rectum and psoas spasm attending a lesion which otherwise is recog-

nized as a suppurative one warrants extraperitoneal exploration after a period of observation leads to the belief that an iliac abscess probably exists. From personal experiences it can be stated that pus will in all probability be encountered in such an exploration. It should be emphasized that reference is not made here to pelvic abscesses derived from the uterus and adnexa, bladder, prostate, or rectum, which are characterized by pelvic masses discernible by local and bimanual examination and for which rectal, vaginal, inguinal or other forms of local drainage may be indicated. These cases belong to the pelvic form of retroperitoneal (extraperitoneal) abscess which, as stated at the outset, are omitted from discussion in this presentation.

Obviously the surgical approach for an extraperitoneal abscess is extraperitoneal, yet in this group of 23 cases the peritoneal cavity was deliberately traversed in four. This not only reveals the margin of error in diagnosis but also serves to emphasize the necessity of being prepared for the surprise of encountering an extraperitoneal abscess when an intraperitoneal one was anticipated. Death from peritonitis will be avoided if the well known safeguards to avoid general peritoneal contamination are taken should the abscess be entered inadvertently, or, when the lesion is found to be extraperitoneal before pus is encountered, if a new incision is made for its extraperitoneal approach. The fact that neither of the 2 deaths in this series of 23 cases occurred among the 4 transperitoneal operations attests to the accuracy of the foregoing statement. In most of the retroperitoneal operations an inguinal incision was made; the incision was a low rectus one or was placed above the iliac crest in a number of cases. An inguinal incision placed either medially or laterally in accordance with the known or assumed site of an iliac abscess appears to be ideal for the purpose. It has the great advantage of being capable of liberal extension in either direction (more particularly laterally and upwards) in order to expose fully a deeply placed abscess or to explore for a suspected abscess. It may not be amiss to refer to a few personal experiences in which exploration, apparently negative, was almost discontinued only to encounter pus on or even medial to the psoas muscle. Only a liberal incision makes possible an adequate (and safe) exploration of the iliac retroperitoneal space. The inguinal incision which I employ is placed directly above and parallel to Poupart's ligament, traverses the external oblique aponeurosis, some muscular fibers, and the transversalis aponeurosis. Thereby the lateral portion of the inguinal canal is laid open. The peritoneum, bared automatically after the transversalis is traversed, is stripped upward and medially away from the underlying iliacus muscle. At this stage, or at a later stage in deeper or more medially placed abscesses, the evidence of an inflammatory mass is encountered. As already suggested, if necessary the incision is enlarged in the appropriate direction in order to expose adequately the region of the abscess. At times the incision should be enlarged *after* the abscess is entered for the purpose of establishing adequate unroofing and drainage.

In the discussion of lumbar retroperitoneal abscess emphasis was placed on the desirability of full operative visualization of the abscess cavity and its

recesses, and, with this achieved, gauze tamponade for drainage. In the case of iliac abscess the necessity for such operative management is even greater because the abscess usually is more deeply situated and, inadequately cared for, is more prone to be followed by local complications and sequelae. Indeed the anatomical difficulties in the way of adequate drainage may be so great or the ramifications of an advanced lesion so widespread that recurrence (or persistence and recurrence) can be anticipated unless a complete operation is performed. Thus there was one case which required several operations performed over a number of years and a final result was not obtained until the psoas was transected for the drainage of an abscess on its medial aspect. In another case in which the area of suppuration was widespread a second extraperitoneal drainage directly above the primary one was necessary about a year after the original operation (with an intervening period of complete good health and normal function).

Although the difficulties above referred to make for complications and sequelae (high morbidity) after operations for iliac retroperitoneal abscess the mortality is low, 2 deaths in 23 cases.

The following is the report of the case already referred to, one in which extraperitoneal suppuration followed a vaginal pelvic operation. The patient presented the picture of an advanced peritonitis at the time she came to retroperitoneal drainage but the case is unique in that the iliac retroperitoneal suppuration was bilateral. The case also is of interest because of the opportunity to learn through another operation many years after the bilateral operation for retroperitoneal abscess, that a quite unsuspected tubal suppuration had followed the original pelvic operation.

#### CASE REPORT

*History:* (Adm. 378340). Mrs. M. M., 36 years old, was admitted to The Mount Sinai Hospital April 1, 1935, for a vaginal operation for prolapse of the uterus and cystoectocele. The bladder was stripped to the peritoneum in the customary manner, the peritoneal cavity was entered and a small fibroid on the anterior wall of the uterus was removed. Both tubes were ligated. A Fothergill repair was performed in the customary manner but in reefing the pubocervical fascia it was noted that the tissues were thin and friable. The operation was terminated by an extensive anterior and posterior colporrhaphy. The postoperative course was satisfactory until the tenth day after operation. The temperature became progressively elevated, associated with pain in both iliac regions. Abdominal distention soon became a prominent feature. The pelvic examination revealed induration in both fornices but no mass. On the seventeenth day after operation there was a chill (blood culture taken at that time was subsequently found to be sterile). The following day the fever reached a new high level (105°F.), and there was then noted pronounced tenderness and induration in both iliac regions. The blood examination was characteristic of suppuration, with a white cell count of 34,100, of which 96 per cent were polymorphonuclear leucocytes. It was the opinion of the operating gynecologist as well as of two gynecologic consultants that the clinical picture was referable to an inflammatory exudate and that operation was not indicated. However, it was also agreed that an exploration for pus was not contra-indicated in view of the patient's desperate condition.

*Operation:* (20 days after Fothergill repair.) A left lower inguinal incision was made which was deepened through the external oblique aponeurosis and musculature. The

peritoneum which was visualized was edematous; it was stripped mesially exposing the iliac vessels. There was then encountered a collection of pus under tension. The lateral extremity of the incision was extended upward because the suppurative tract was found to have reached up to the lumbar retroperitoneal space. Further retraction of the peritoneum revealed the full extent of the suppurative tract which rose from the pelvis and reached to the lower border of the left kidney. In addition to 6 or 8 ounces of pus in the abscess the tract was lined with thick purulent exudate. It was packed widely.

In view of the persistence of tenderness and resistance in the *right* lower quadrant uninfluenced by the drainage of the left sided abscess, the likelihood of an additional collection of pus in the right pelvic retroperitoneal space led to the decision to explore the right retroperitoneal space the day after the left sided drainage had been instituted.

Accordingly, a right-sided incision parallel to and immediately above Poupart's ligament was made and was deepened to the peritoneum as on the left side. Here too a collection of pus in the pelvic retroperitoneal space was encountered. The incision was enlarged upward as on the left side but not to the same extent because on the right side the collection of pus was more limited to the pelvic region. The abscess contained about 8 ounces of pus. As on the left side, all recesses of the abscess cavity were packed with iodoform gauze. *Enterococcus* was grown in culture of the pus.

*Course:* After drainage of the abscesses the general condition rapidly improved and the patient was convalescent in a short time. However, some abdominal distention persisted for several days. The temperature was normal after the first postoperative week. The patient was discharged 16 days after the drainage operations with clean granulating wounds. In a few weeks the wounds were healed and the patient was largely symptom-free.

The follow-up continues from that time (1935) to the present. Throughout this period there were vague symptoms referable to the pelvis. At times these became more precise, consisting of acute discomfort in the lower abdomen, chiefly in the left lower quadrant, which would last for a number of days. Under the care of and on the advice of a gynecologist the patient received conservative treatment but finally an artificial menopause was induced because of persistent pain, and other symptoms referable to the adnexa.

The patient again came under my observation on July 17, 1942 as an acute emergency. For several weeks before this time there had been occasional abdominal pains similar to those above described. However, they became increasingly more severe and were accompanied by some fever. For two days before admission fever was high and there was severe sustained lower abdominal pain and abdominal distention.

On physical examination the patient was noted to be profoundly prostrated, with rapid pulse, temperature of 104°F. and moderate abdominal distention. There was rigidity of both lower recti, much more marked on the left side. Here there was direct tenderness on moderate pressure. By vaginal examination there was found a tender mass in the cul-de-sac which extended to the left. Under anesthesia an obvious mass in the left lower quadrant could be felt upon bimanual examination. At operation, which was performed shortly after the patient was seen, free pus was encountered upon opening the peritoneal cavity. Adherent omentum was released and the free peritoneal cavity was packed off. Several collections of pus were encountered about a mass which was adherent to the pelvic peritoneum. This mass when isolated was found to be a pyosalpinx. Its mesial end appeared to be detached from the uterus or was adherent to it by a fibrous band. Its distal end was embedded in the posterior peritoneum as was the remainder of the tube to a lesser degree. The tube was freed chiefly by dissection and the bare deperitonealized area was drained by a gauze pack placed down to it and brought out through the lower end of the abdominal incision. The gauze pack was surrounded by a rubber dam. The microscopic report on the removed tube was chronic and acute salpingitis.

The postoperative course was essentially uneventful. The general condition has improved progressively since operation and it is fair to assume that the cause of the prolonged semi-invalidism was chronic infection of the left tube. Judging by the situation of the tube at the time of operation it can be assumed that the same factor which led to the infection of the tube led to infection of the contiguous extraperitoneal spaces.

## RETROPERITONEAL PHLEGMON

*(Diffuse Retroperitoneal Cellulitis)*

This lesion which stands out in striking contrast to the previously described lumbar and iliac abscess was encountered in 17 cases. It resulted from a variety of causes, the most common (6 cases) being acute retrocecal (or retroperitoneal) appendicitis. In further contrast to abscess the cause of the lesion can almost always be stated with precision. The infection is encountered only in adult life (compare with abscess). The main contrast with retroperitoneal abscess, however, consists not only in the high mortality of retroperitoneal phlegmon but also in the limited outlook for relief by surgical drainage. In view of the introductory remarks at the outset of this contribution it is proper to call attention to the one case of post-abortive endometritis and parametritis among these 17 cases. One may assume that retroperitoneal phlegmon would be more frequently encountered in gynecologic clinics to which post-abortive and post-partum infections are more frequently admitted.

The essential feature of the pathology of retroperitoneal phlegmon is an infiltrative, necrotizing, poorly-limited inflammation of the cellular retroperitoneal tissues. Fibrinopurulent or necrotic exudate and small pools of pus are to be encountered in the phlegmonous process whose great extent (as well as ill-defined limits) is characteristic. The infection extended to or beyond the diaphragm into the mediastinum in the majority of instances. It extended downwards into the perineum and even into the thigh in a number of cases.

In contrast to the bacteriology of retroperitoneal abscess that of phlegmon is characterized by the predominance of bacillus coli which was found as the sole organism in 7 cases, and in combination with other organisms in 4 other cases.

The symptomatology in the early phases was quite indistinguishable from that of the causative infection—appendicitis, renal infection, regional ileitis, pancreatitis, parametritis, etc. Only with the development of lumbar pain or pain radiating down the thigh, hip spasm, or spread of pain from the sites to which it had previously been localized, could a retroperitoneal spread of infection be suspected.

On physical examination the essential findings were those of the underlying disease. However, diffuse spread into the retroperitoneum was suggested by such signs as lumbar tenderness in cases of appendicitis, tender lumbar mass in cases derived from the kidney or colon, or lumbar tenderness in parametritis. There were two general features which could be regarded as suggestive of a diffuse retroperitoneal infection: first, the patients were ill out of proportion to the manifestations ordinarily referable to the causative infective focus; secondly, pronounced abdominal distension was common. The diagnosis of retroperitoneal phlegmon was not made in the majority of instances and, when made, its extent and ominousness was not often appreciated.

Operation was performed in most of the cases but all died whether or not they were operated upon. The impression is gained from a study of these cases that the only ones in which there may be an outlook for operation are the appendicitis group. It is possible that wider and early retroperitoneal drainage

for these cases might achieve better results. It also is possible that chemotherapy in conjunction with surgical drainage of foci of suppuration might result in occasional cure of an otherwise fatal infection. The contrast between retroperitoneal phlegmon and abscess is so extreme in every aspect that the cases are grouped together only because they have a single feature in common—a pyogenic infection of the retroperitoneal connective tissue.

## THE BEGINNINGS OF UTEROTUBAL INSUFFLATION

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The anniversary volume dedicated in honor of Dr. Hiram N. Vineberg affords me the privilege and opportunity of recording some of the circumstances connected with the beginning of uterotubal insufflation as a nonoperative clinical test for tubal patency. The occasion is peculiarly fitting, I feel, because the test was devised during the period when Dr. Vineberg was Attending Gynecologist at The Mount Sinai Hospital, and was tried not only with his consent but with his generous encouragement and cooperation. Were it not for his support the test might have made its way much more slowly, for it seemed at first so radical that conservative gynecologists might well have hesitated to give it their approval. Even after being enthusiastically received by many at its first presentation before the Section on Obstetrics, Gynecology and Abdominal Surgery at the Seventy-first Annual Session of the American Medical Association at New Orleans in April, 1920, it was still regarded in some quarters as highly revolutionary.

With my appreciation for Dr. Vineberg's help, it is a pleasant duty to record the stalwart support freely given by some of his colleagues, Fellows of the American Gynecological Society: Dr. Reuben Peterson, Dr. Robert L. Dickinson, Dr. George Gray Ward, Dr. Brooke M. Anspach, to name only a few of the leaders in the field of gynecology who helped to establish the method as an accepted diagnostic procedure.

It is with the deepest feeling of gratitude that I remember the immediate approval with which Dr. Vineberg received my suggestion. It was late in October, 1919, that I first proposed the method that would determine the existence of tubal patency or nonpatency by introducing oxygen into the uterus both without and with controlled pressure, thereby doing away with the need of an exploratory laparotomy to determine the facts. I cannot forget the warm encouragement of his reply. "The idea," he said, "is entirely new to me, but I have confidence in you. I hope your preliminary work has been adequately prepared and that you will undertake the test clinically with all due precautions for the patient's safety. I shall stand behind you."

Considering the unprecedented procedure which I was contemplating, I can only now appreciate what those words meant to me in the course of the next few years. Opposition developed, particularly here at home, but also in some places abroad. But Dr. Vineberg's protective influence and encouragement enabled me to go on exploring the possibilities of my method. On more than one occasion he gave me wise counsel mingled with admonitions for the safety of the procedure. "Guard it," he told me, "as if it were your child."

I record these facts with high admiration for Dr. Vineberg, both as teacher and as scientist. Acknowledged one of the most brilliant diagnosticians in gynecology of his time, he not only initiated me into precise methods of diagnosis,

he stimulated in me a deep respect for accuracy and intellectual honesty. Elsewhere in this volume it is shown that his "batting average" as a diagnostician was as high as is humanly possible, but Dr. Vineberg never failed to admit mistakes in diagnosis or errors in judgment. The rigid discipline and self-criticism that characterized his work made these, to be sure, few and far between. But how salutary even these were in inspiring members of his staff, those of the intern staff, and the very visitors who heard him, to aspire to his high standard of integrity! It was therefore natural that when I left The Mount Sinai Hospital in January, 1909, to go abroad for further training and postgraduate study, Dr. Vineberg's influence directed me toward the special field of obstetrics and gynecology.

During the following decade the need for a clinical nonoperative method of determining the patency of Fallopian tubes continued to weigh upon me, as it must have on many others at the time. It had been observed that the efforts of surgery to correct sterility had resulted more frequently in failure than in success. In those days, when a married couple who desired children remained childless for several years despite the fact that they had used no contraceptive, it was more apt to be the wife than the husband who consulted the family physician or gynecologist in the hope of learning the cause and discovering a remedy for her involuntary sterility. The examination, as a rule, therefore, was limited to her, the husband receiving scant if any attention. The investigation of the patient usually consisted of a gynecologic examination upon which diagnosis, prognosis and therapy were based. The results were often contrary to the prognosis given. Many women whom the specialist's opinion doomed to barrenness soon became pregnant, whereas others who were told there was nothing wrong with them remained sterile.

Among the reasons for the failure of surgery to cure sterility was the then prevailing notion that it was due chiefly to mechanical obstruction of the cervical canal and to other cervical abnormalities. Therefore, surgical therapeutic measures were misdirected. The part played by the male partner was not yet fully appreciated. His share in sterility and the concept of a sterile mating, now too obvious for emphasis, were first realized in the second decade of the present century.

It was a common experience of gynecologists to meet with disappointment after a discission operation, dilatation of the cervix and curettage, the insertion of stem pessaries, and other similar measures. The reason for this failure was that the Fallopian tubes were the actual seat of obstruction. Without knowledge of the tubal status a reliable prognosis could not be formulated.

The failure of the aforementioned, otherwise excellent, operations was gradually realized to be due to the possibility that the Fallopian tubes may have been nonpatent. Frequently the Fallopian tubes, though occluded, were not found on palpation to be appreciably enlarged. In many cases gross evidence of a pelvic inflammation was not present to direct suspicion toward implication of the tubal lumen. In cases where frank pelvic inflammation was present, acute or chronic, it was natural to suspect that the tubes were diseased alone or with the

ovaries. Nevertheless, even with a reliable history of an antecedent pelvic inflammation, it was impossible to preempt tubal patency, for spontaneous restitution had sometimes been observed by older gynecologists and clinicians. It was clear that opinion as to the patency or nonpatency of the Fallopian tubes was at all times mere guess work.

To fill this gap in diagnosis and prognosis, an exploratory laparotomy was deemed indispensable and was accordingly advised. But, notwithstanding advances in asepsis, anesthesia, and surgical technique, all of which made laparotomy safer, the operation was still regarded as a formidable procedure to resort to for the single purpose of ascertaining whether the uterine tubes were open or closed. Surgeons naturally hesitated to urge abdominal exploration to determine the status of the Fallopian tubes except in rare instances when the desire for offspring was intense.

The urgent need for a nonsurgical method of ascertaining the presence of open or closed Fallopian tubes was forcibly brought home after several disappointments in cases where a cervical operation had been performed. One morning in 1913, I had occasion to operate upon two patients for the relief of sterility. A prognosis was not rendered because the tubal factor was unpredictable. As the recommendation of an exploratory laparotomy was not accepted by either patient, a Pozzi operation was done. One patient became pregnant within six months, the other remained sterile. The disappointed patient later developed some abdominal pain. Seeking other opinion, she was informed that her uterine tubes were inflamed as the result of the operation.<sup>1</sup> This experience increased my efforts to find a nonoperative test for tubal patency.

Certain x-ray opaque substances which were being employed in urology seemed to offer a possible solution. The same media, I thought, might be used in the gynecologic field. I had, however, to consider the hazards of invading the peritoneal cavity by way of the uterus, a procedure which had no precedent. Although the self-defensive powers of the peritoneum were already understood, the possible effects upon the uterus and the Fallopian tubes could not as yet be predicted. Curettage, which was commonly and more or less indiscriminately employed, had laterally become restricted to instances of postabortive bleeding and to cases of suspected uterine malignancy.

The introduction of a foreign substance into the uterus and thence through the tubes into the peritoneal cavity was a new venture. It was supported and encouraged chiefly by the increasing acceptance of Hitschmann and Adler's discovery that the endometrium undergoes cyclic changes which were commonly mistaken for endometritis, and that endometritis as such was a rarity, the uterine cavity in the nongravid state being practically always free from infection except in acute gonorrhea.

Before Hitschmann and Adler's demonstration, the use of a uterine sound was as violently assailed by some gynecologists as it was tenaciously advocated by others. The newer knowledge disarmed the fears of those at least who would

<sup>1</sup> This patient returned several years later to have her Fallopian tubes insufflated. She proved to have tubal patency and conceived shortly afterwards.

venture uterine exploration with a cannula through which x-ray opaque solutions might be injected. Of all the solutions then in vogue, collargol appeared to have the greatest appeal. It was allegedly aseptic; it was x-ray opaque and had even been used extravascularly in puerperal sepsis. Accordingly collargol was the first substance to be considered for its use in gynecology.

My work with collargol was begun in late January 1914 at the laboratory of Professor E. Wertheim, II Universitäts-Frauenklinik in Vienna under the directorship of Professor J. Schottlander. Previous anatomic studies had given me an idea of the shape and capacity of the uterine cavity. The collargol injections were made in the dead human uterus and in living rabbits. A preliminary report pointing out the possibilities of diagnosing submucous fibroids was sent to the *Zentralblatt für Gynäkologie*, where it appeared on May 4, 1914.<sup>2</sup> In this paper it was mentioned that a more important object was contemplated, namely, the proof of tubal patency by the use of radiopaque solution. I was unaware at the time of Cary's publication, which was the first in America bearing upon the use of collargol for testing the patency of the Fallopian tubes. His work had been published in March, 1914.

The serious objection to chemical opaque solutions then in use was the possibility that they might transfer infective material from the genital tract to the peritoneal cavity. Whether or not such solutions possessed adequate antiseptic properties to prevent peritoneal inflammation was a debatable question. In any event, a chemical reaction, it was believed, might produce undesirable effects, notably upon the mucous membrane of the tubes, thus resulting in an occlusion where a normal lumen was previously present.

From my clinical experience with collargol injection, the results of which were reported in April, 1915,<sup>3</sup> two features presented themselves which soon made me realize that its use was undesirable for clinical purposes. They were colic attending and following the injection; and peritoneal irritation in cases with patent tubes. From the limited experience with collargol the conclusion reached was that it might be used in occluded tubes, in which case, if damage resulted, the patient suffered no further reproductive loss. The risks entailed would ensue from possible infection. If, however, the tubes happened to be patent one had to reckon with the possible loss of fertility. Substitution of thorium nitrate, and later of bromide and iodide solution for the collargol, which I employed in a number of cases, was intended to eliminate inspissation. But these either failed in this respect or had other disadvantages.

The ideal medium which would enable one to determine tubal patency without the necessity of a laparotomy was, therefore, still lacking.<sup>4</sup> When the value

<sup>2</sup> The translation of my paper into German was made by my good friend Dr. Joseph Novak, who worked in the same laboratory and is now associated in my service at The Mount Sinai Hospital.

<sup>3</sup> X-ray Diagnosis in Gynecology with the Aid of Intra-uterine Collargol Injection. *Surg., Gynec. & Obst.*, 21: 435, 1915.

<sup>4</sup> The adoption in the last decade of the crystalloid iodine solutions first presented by M. Swick in uroselectan, such as skiodan, diodrast, and hippuran, has overcome many of the disadvantages of the older solutions of the halogen group. It is probable that in visco rayopaque a close approach to the ideal radiopaque medium has been achieved.

of pneumoperitoneum as a diagnostic method was demonstrated, it occurred to me at once that oxygen might be the long-sought agency for the specific purpose of diagnosing tubal patency. If, instead of solutions, a gaseous medium could be introduced into the uterus, it might produce an artificial pneumoperitoneum, but only if the Fallopian tubes were patent.

The harmlessness of oxygen in the peritoneal cavity had already been established by a number of observers, and records of oxygen injected by abdominal puncture were at hand to support their contention. The great advantage in the use of this gas was that it was aseptic and carried no appreciable amount of infective material in suspension, and that when the patient stood up it rose almost immediately to the region of the diaphragm. If any infective material chanced to be carried by the oxygen, it would probably reach the subphrenic space, and any inflammation that might result would at least not affect the tubes. Artificial sterility would therefore be avoided. The passage of gas through normal tubes would, moreover, leave no chemical residue within their lumen. That the gas would become absorbed very rapidly by comparison with the chemical solutions then in use was a further advantage. Should the gas fail to reach the peritoneal cavity, tubal occlusion would be diagnosed. No harm could possibly be thus produced, because on meeting an obstruction in the tubes the gas would regurgitate during the injection or be expelled upon removing the cannula. The slight amount remaining within the genital tract would be more rapidly absorbed than would be true of irritating solutions. This was found to be so, and more especially when carbon-dioxide was later substituted for oxygen.

The production of a subphrenic pneumoperitoneum by way of the uterus definitely established the patency of the Fallopian tubes.

The first examination by uterotubal insufflation with oxygen took place on November 3, 1919, in the x-ray department of The Mount Sinai Hospital of New York City. The quantity was measured roughly by gauging the number of bubbles passing through the wash bottle per minute. The intrauterine pressure was not controlled by a manometer; the gas was allowed to enter the peritoneal cavity until a moderate amount of visible abdominal distention resulted.

Having had no previous clinical experience in this field, we naturally had to wait for developments. Theoretically we expected to see the abdominal wall rise in case the oxygen gas succeeded in gaining access through open tubes into the abdominal cavity. Those were indeed tense moments as Dr. Pere Lund, Dr. Harry Wessler, Dr. Arthur J. Bendick, and others of Dr. Jaches' roentgenologic department who happened to be present, were observing this first patient through whose uterus I ventured to insufflate oxygen. The actual rise of the abdominal wall was corroborated by everyone present. This constituted first-hand proof that the oxygen actually passed through the tubes and into the peritoneal cavity. Nevertheless it was deemed necessary to establish the presence of the oxygen gas in the abdominal cavity by subjecting the patient to fluoroscopy and radiography. In every respect the x-ray evidence was the same as that which was obtained when oxygen had been introduced into the peritoneal cavity by direct abdominal puncture.

The patient, having been insufflated with several liters of oxygen, was com-

fortable in the recumbent posture, but we noticed that she had great epigastric distress and severe shoulder pains when she stood up before the radiosopic screen. She was kept on her back for a little while and, as she was ambulatory, was brought home about one hour later and put to bed with the foot of the bed elevated. This gave her tolerable comfort. The discomfort rapidly disappeared so that at the end of the third day she was able to report to the x-ray department complaining only of slight uneasiness in the shoulder regions. A small amount of oxygen was still present under the diaphragm. The patient became gravid within two months after the insufflation and was delivered of a full-term baby; one and a half years later she gave birth to her second child.

Though success attended this first case, it was necessary to establish several facts before the method warranted a preliminary report. Accordingly, in the next thirty or more uterotubal insufflations particular attention was paid to the following: 1) the patient's tolerance to this diagnostic method; 2) the minimum volume of oxygen necessary to produce a subphrenic pneumoperitoneum which could be demonstrated by fluoroscopic examination or diagnosed by the telltale and tolerable shoulder pains; 3) the possibility of infection; 4) the danger of embolism; 5) the interpretation of the findings and their reliability in diagnosis. The indication for the application of the test was clearly specific. The contraindications were based upon general gynecologic and medical experience and were modified as a result of the observations made in these early cases.

The preliminary observations showed that the patients stood the examinations with little discomfort. When oxygen was insufflated in amounts of 100 to 200 cc., the symptoms were relatively slight and did not interfere with the patient's daily routine. No after effects were noted in the pelvis subsequent to the gas insufflation.

As carbon-dioxide was found to be more rapidly resorbed than oxygen in equal quantities and thereby also minimizing the shoulder pains and epigastric discomfort, it was early adopted as the gas of choice for uterotubal insufflation. The danger of gas embolism was also eliminated by carbon-dioxide insufflation because, if intravasation occurred despite all precautions, it would be immediately dissolved in the blood stream. Oxygen, like air, being less soluble, carried the theoretical and actual danger of air embolism. Against this danger safeguards were provided in the insufflation apparatus which consisted of a carbon-dioxide tank with regulating and reducing valves, a volumeter and a blow-off valve.

In addition to these safeguards and the prescribed indications and contraindications previously mentioned, special emphasis was laid upon the various steps of the technical procedure. The object of these precautions was to avoid accidents and untoward sequelae which might result from faulty technique. From the earliest stages of its development the aim has been to make the test accurate and safe.

The apparatus was shortly thereafter (1925) improved by a kymograph thus providing a method of precision in determining tubal patency and nonpatency and at the same time increasing its safety. By means of this apparatus it

became possible to demonstrate graphically the functional status of patent Fallopian tubes and in cases with impaired patency the varying degrees of tubal strictures and adhesions.

The nonoperative test for tubal patency appeared to have aroused interest soon after its preliminary report in April, 1920. The latter was based upon 55 cases. A fuller report of this work, based upon 70 cases, including 33 who were insufflated with manometric control, was read at New Orleans and published in the *Journal of the American Medical Association* in September, 1920. It was soon followed by the publications of Peterson (August, 1921), Furniss (November, 1921), Dickinson (August, 1922), J. Novak (1922), Rongy (1922), Sellheim (1923), and many others. It became known as the Rubin test soon after the publication by Furniss, who first gave it this designation.

## LEFT PELVIC MASSES

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In honoring Dr. Hiram N. Vineberg for his conspicuous efforts in the field of gynecology, by contributing an article to his Anniversary Volume, I am led to choose a topic which will be of mutual interest to internists and to the pelvic surgeon. Inflammatory and neoplastic masses, recognizable by bimanual palpation are often confusing and difficult to evaluate. The possibilities are many, the means at our disposition for their identification often only too limited. Not alone is man finite, not only is medicine an applied rather than a true science, but the most ideal instruments of precision often fail us in our greatest extremity.

Instances in clinical practice are many, where the diagnostician, so-called, and the internist and the surgeon have met in the common ground of the lower left pelvis to discuss, to debate and to try conclusions on the real identification and nature of such a mass.

A young woman of thirty-four years presents herself with the history of fever, emaciation and a tender mass in the left quadrant of the abdomen. The mass is palpable by rectum and is easily identified through the relaxed abdominal wall. The diagnosis of a salpingitis, a twisted ovarian cyst, or of a sigmoiditis, is made and operation is indicated. No pointing symptoms referable to the intestinal tract are significant; the irregular menses are consonant with a lesion of the generative organs or might occur in any lower severe abdominal disease with weakness and with inanition. To the surprise of the operating surgeon the mass at laparotomy is determined as originating in a lower or terminal ileitis with fistulous communications to the sigmoid or pelvic colon. In the emergency an ileotransverse colostomy is performed, but without transection of the ileum below the anastomosis, an operation which is not satisfactory, and one which must lead eventually to a second more radical resection of the cecum and terminal ileum and of the ileitis.

The appearance of ileitis as a mass in the left pelvis is unusual but does occur both in the female and in the male. When seen in the acute phase, with fever and inanition, when the outstanding symptom of diarrhea is lacking, the diagnosis is most difficult. For atypical ileitis not infrequently is associated with constipation rather than with diarrhea, and under such circumstances, the only method for precise diagnosis, the x-ray is often omitted. And, if not omitted, the radiographic changes may be so atypical, and so little distinctive, that extra-intestinal pressure effects rather than true ileitis is often suggested. Instances have even been encountered wherein external abdominal wall fistulae have occurred and have been interpreted as originating in actinomycotic or tuberculous lesions, or in perforating adnexal inflammatory foci rather than in the less suspected but more likely ileitis with its characteristic meandering fistulous tracts.

<sup>1</sup> From the Medical Services of The Mount Sinai Hospital, New York.

Another cause for great confusion arises when a low firm pelvic mass, with fever and inanition occurs in an elderly woman with the characteristic radiographic signs of diverticulitis. Diverticulosis, or the visualization by x-ray of diverticulae of the pelvic colon occurs in presumably 25 per cent of adults over middle age. Let any febrile or inflammatory lesion arise in the lower left pelvis, and let diverticulae be demonstrable radiographically, and the non-sequitur conclusion of diverticulitis with abscess formation and peri-sigmoiditis seems the obvious and the likely one. The first true differentiation should be made between a carcinoma of the sigmoid with perforation and a diverticulitis with perforation and abscess. Such a differential diagnosis is anything but easy. By either abdominal or pelvic-rectal examination the mass is palpable as firm, hard and tender; fever is present in both conditions, as is severe emaciation and progressive loss of weight. Nothing about the mass differentiates the benign from the malignant possibilities. Nor is the radiography competent of making the decisive pronouncement, because, just as in the gastric lesions the benign and the malignant are impossible to differentiate, so in the pelvic colon it is often beyond the scope and limitations of the most experienced radiographer to determine the exact etiology of the underlying pathology.

It is a mistake to think of carcinoma of the sigmoid, coexisting with diverticulosis as a degenerative or malignant metaplasia resultant from the presence of inflammatory diverticulae. Such malignant degeneration is at best a very rare phenomenon if it occurs at all.

In one such an instance the debate ran high, unfortunately over a course of weeks, as to the true nature of a large inflammatory mass in the left lower quadrant of a woman of sixty-four years of age. The x-ray showed diverticulae of the sigmoid, the mass coexisted in anatomic site with the pelvic colon, fever was high, the mass increasing steadily in size. Carcinoma of the colon seemed radiographically most unlikely; an old coronary seizure made operation apparently inadvisable. The best and most experienced physicians and surgeons agreed with one mind that diverticulitis with abscess was the correct diagnosis and that the proper course was that of conservative watchfulness. After several weeks of coordinated delay operation was forced by the appearance in the abdomen of free peritoneal fluid. At laparotomy a carcinoma of the left ovary was discovered adherent to and invading the mass of the pelvic colon. Diverticulitis with inflammatory abscess is not an operative condition under the best of circumstances; the logical delay and the complete lack of suspicion that the left ovary might be involved created an extremely unhappy situation.

When a mass becomes palpable in the posterior cul-de-sac in an older female, the mass situated anatomically between the posterior surface of uterus and the anterior surface of rectum, then clinical experience and the *tactus eruditus* of the examining finger alone must differentiate the two conditions. Most such masses are truly myomata of the uterus projecting posteriorly into the fold of Douglas. Unhappily hysterectomy is occasionally performed before all the possibilities of diagnosis have been exhausted. Diarrhea, or the passage of blood per rectum may be absent or may be so minimal as to be overlooked. Only after the hyster-

ectomy does the continuance of pain and discomfort create a situation requiring renewed investigation. Nor for the first time does the diarrhea and the appearance of blood with the fecal passage seem significant. The sigmoidoscopy, with the barium enema, but particularly the sigmoidoscope, tell the story of a carcinoma of the recto-sigmoid.

Apparently in the course of the technical removal of a fibroid uterus at operation a recto-sigmoid carcinoma can be easily overlooked. For such a prolapsed tumor lying low in the cul-de-sac can easily escape detection during the bleeding and the manipulations associated with a hysterectomy. Radiography is often deficient, for the compression of the recto-sigmoid by a large fibromyomatous mass originating from the uterine body simulate closely the defect of an intrinsic neoplasm of the colon. Here the possibilities of sigmoidoscopy are without limit, when the colonic carcinoma is within ten to twelve inches of the anal orifice. Cleverly employed, properly interpreted and supported by biopsy and histologic verification the true nature of the lesion is eventually discernible.

In the routine of the Consultation Clinic at this Hospital the true differentiation between these two likely appearing conditions often poses a most perplexing problem. When both uterine fibroma and sigmoid carcinoma are present, all the skill of rectal and pelvic palpation, plus the sensitive x-ray, plus sigmoidoscopic observation are required for the elucidation of the true nature of the predominant offending lesion.

## THE CLINICAL EVALUATION OF HYSTEROGRAPHY\*

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The introduction of roentgenology in clinical medicine was soon followed by attempts to visualize the outline of the endometrial cavity by Rindfleisch (1) in 1910. Collargol was used as a radiopaque medium for x-ray visualization of intra-uterine pathologic conditions by Leloir (2), Cary (3) and Rubin (4). The halogen salts were also used but were soon replaced by the widely popularized iodized oils, Lipiodol and Iodopine. These iodized oils are superior to previously used radiopaque substances, but they are poorly absorbed and cause mechanical and chemical irritation with subsequent body tissue reactions. In many cases, Lipiodol can be demonstrated in the body years after it has been introduced.

Crystalline iodine compounds (Diodrast and Hippuran) in aqueous solutions were first used for visualizing the kidneys and urinary tract. They are practically non-irritating and are readily absorbed by the body without toxic effects. Their use in hysterosalpingography has been widely employed, but they have the disadvantage of escaping rapidly into the peritoneal cavity, so that a lesion in the uterus may be missed. It then became apparent that if something were added to the aqueous solution of crystalline iodine compounds to increase their viscosity without retarding their absorbability, a more definite visualization of the uterine cavity would be obtained. Neustadter and co-workers added 50 per cent glucose. Titus and his co-workers added gum acacia in 25 per cent concentration. These additions did not give completely satisfactory results. Rubin has used a 3.5 per cent concentration of polyvinyl alcohol in a solution of rayopake. He has reported excellent results with this solution. It is an ideal contrast medium for hystero-graphy, as it is radiopaque, easily and rapidly absorbed, is non-irritant, and has enough viscosity for proper filling and outlining the uterine cavity.

With the gradual development of contrast media for hystero-graphy, diagnostic accuracy of intra-uterine lesions was obtained. At the outset, gross anatomic malformations were visualized (fig. 1). Later, filling defects and irregularities in the outline of the uterine cavity were recognized and correlated with the pathologic conditions found at operation. We can now depend on the hystero-graph, in most cases, to such a degree as to influence and determine the procedure to be used in the cure of the patient. At the same time, the clinical interpretation of the gynecologic signs and symptoms must be carefully evaluated.

Hystero-graphy is indicated in cases where the history and physical findings do not reveal, but lead one to suspect the presence of an intrauterine pathologic lesion, such as an endometrial polyp, submucous fibroma, other intra-uterine

\* Read at a meeting of the Obstetrical Section of the New York Academy of Medicine, April, 1943.

growths and malformations of the uterus. Hysterography is also of value in determining the nature and extent of a surgical procedure when intra- or extra-uterine tumors are present.

The contra-indications to hysterography are pregnancy, active uterine bleeding, gonorrhea or other infections of the genital tract.

The technique of hysterography is simple and can be done with practically no discomfort to the patient. All the precautions of surgical asepsis should be observed. The patient is placed in the lithotomy position on the Squier genito-urinary table. Sterile towels are used for draping the vulva. The x-ray technician makes careful adjustments of the patient's position on the table so that the exposure of the plate will show the lower pelvis. For the average patient, a distance of 30 centimeters, 60 milliamperes, 115 primary volts and 3 seconds exposure are used. A flat plate is taken as a control. The vulva is cleansed with



FIG. 1. Uterus didelphys, patient aged 39 years

a bichloride of mercury sponge and the vagina and cervix exposed by a bivalve speculum. The cervix is cleansed with a dry sponge, painted with a 5 per cent tincture of iodine and grasped with a tenaculum forceps. The radiopaque substance, viscorayopaque, is drawn up in a syringe to the 10 cc. mark and a uterine canula such as is used in the Rubin utero-tubal insufflation test, is attached to the syringe and held upward. The plunger of the syringe is pushed up, displacing the air in the canula, at the same time filling it with the radiopaque substance. The canula is then introduced into the cervix to a point a little above the internal os. Two cubic centimeters of solution are injected into the uterus and an x-ray picture is taken. Two cubic centimeters more are injected and another picture is taken. If the uterus is not appreciably enlarged this amount of solution divided between the two exposures should be sufficient for good visualization of the uterine cavity. However, the amount and the number of exposures may be varied in large uteri, or in cases where tubal visualization is also desired. Over filling of the uterus with contrast medium may obscure small uterine

lesions, as the density of the radiopaque solution may diffuse or cover their outline (figs. 2 and 3).

Before the uterine canula is removed, the plunger of the syringe should be drawn outward to aspirate the contrast medium. This is followed by insufflation of 20 cc. of carbon dioxide gas and another x-ray picture is taken. This gives a



FIG. 2. Outline of a small submucous tumor. 2 cc. of opaque medium used



FIG. 3. Outline of the submucous tumor shown in Fig. 2, overshadowed by 4 cc. of opaque medium.

linear definition of the uterine cavity and its irregularities (fig. 4). All instruments are then removed and a small piece of gauze is inserted into the vagina. The patient should be allowed to rest on a couch or bed for about one hour, as excess spilling of the radiopaque material into the peritoneal cavity may give the patient some discomfort. This soon passes off as the viscorayopake is usually absorbed in about one-half hour.

Our experience with hystero-graphy is based on over three hundred cases done

on the gynecological service of Dr. I. C. Rubin at The Mount Sinai Hospital. This report concerns itself with seventy-two private cases done at The Mount Sinai Hospital by the essayist. It is hoped that a review of this small group will illustrate the value of the method for accuracy of diagnosis and as an aid in determining the therapeutic procedure.



FIG. 4. Outline of the tumor shown in Fig. 2, after carbon dioxide gas insufflation



FIG. 5. Menorrhagia, patient aged 37 years. Uterus the size of a small orange showing submucous fibromyoma 5.5 cm. in diameter. Supravaginal hysterectomy.

The analysis of the seventy-two cases is grouped according to the predominant clinical symptom, i.e., menorrhagia, metrorrhagia, menometrorrhagia, dysmenorrhea, abdominal pain and sterility.

Twenty-two patients with the main symptom of menorrhagia showed positive hystero-grams in eleven instances, or 50 per cent. Four showed submucous fibroids two of which were treated by supravaginal hysterectomy (fig. 5), one by

myomectomy and one by vaginal hysterectomy (figs. 6A and 6B). Four showed endometrial polypi (fig. 7). Three were treated by curettage and one, a rather large polyp, by vaginal hysterotomy (fig. 8). A supravaginal hysterectomy was performed in one case where the uterine cavity showed a uniform enlargement on hysteroqram. This proved to be adenomyosis. In one case a bizarre picture



FIG. 6A. Menorrhagia, patient aged 34 years. Normal size uterus showing submucous bromyoma one inch in diameter. Hysterectomy.



FIG. 6B. Linear definition of the tumor shown in Fig. 6A after carbon dioxide insufflation.

was obtained which made us suspicious of a fundal carcinoma (fig. 9). This was confirmed by curettage and subsequent vaginal hysterectomy. Eleven cases did not reveal any pathologic findings on hysteroqram and curettage showed changes such as are seen in functional bleeding.

The hysteroqram on twelve patients complaining of metrorrhagia showed no filling defects. Nine were curetted and the negative hysteroqram findings were confirmed. The three remaining cases were treated by non-operative measures.



FIG. 7. Menorrhagia, patient aged 37 years. Normal size uterus showing 1 polyp in left horn. Curettage.



FIG. 8. Menorrhagia, patient aged 34 years. Normal size uterus showing intrauterine defect. Polyp the size of a pigeon's egg removed by vaginal hysterectomy.



FIG. 9. Menorrhagia, patient aged 50 years. Normal size uterus showing irregular filling defect. Curettage and vaginal hysterectomy for carcinoma of the fundus.

Fifteen patients complaining of menometrorrhagia gave positive hystero-grams in four instances or 27 per cent. Two were submucous fibroids, treated by supravaginal hysterectomy. One had multiple fibroids and was treated by myomectomy (fig. 10). One showed an endometrial polyp which was removed



FIG. 10. Menometrorrhagia, patient aged 40 years. Uterine cavity irregular in outline because of fibromyomata (eight to ten weeks in size). Myomectomy.



FIG. 11. Dysmenorrhea and menometrorrhagia, patient aged 44 years. Slightly enlarged uterus showing two submucous fibromyomata. Supravaginal hysterectomy.

by curettage. Eleven with no gross pathologic hystero-gram changes in the endometrial cavity were treated by curettage.

Eight cases complaining of dysmenorrhea with no clinical evidence of an etiologic factor and who did not respond to the usual conservative methods of treatment were examined by hystero-gram. Five in this group showed submucous fibroids. One was treated by myomectomy, two by supravaginal hysterectomy (fig. 11) and one by vaginal hysterectomy. One refused operation.

In one case a polyp was demonstrated and was successfully treated by curettage; another showed a uterus bicornis with polypi in both horns (fig. 12). The percentage of positive hystero-grams in this small group was strikingly high—87.5 per cent. This would emphasize the importance of a hystero-gram in dysmenorrhea in a patient who does not respond to the usual medical treatment.

Seven cases of sterility were also investigated by this method. Hystero-salpingography was utilized after the Rubin test had demonstrated closed or diseased tubes. The hysterosalpingograms were made to rule out a co-existent intra-uterine lesion and to determine the site of tubal occlusion. In one who had been treated a long time without success, the hystero-gram finally revealed small submucous fibromyomata.

Hysterosalpingography for diagnosis in sterility is valuable mainly for demonstrating the intra-uterine lesions and gross anatomic changes in the tube, whereas



FIG. 12. Dysmenorrhea and menometrorrhagia, patient aged 35 years. Uterus bicornis with polypi in both horns. Curettage; subsequent pregnancy.

the graph of tubal function obtained by the Rubin test shows not only an occlusion of a tube, but also demonstrates changes in tubal motility due to intra- or extra-tubal pathology. Therefore, in our opinion, the Rubin test is of greater help for recognition of tubal pathology than salpingography.

Four cases complaining of abdominal pain as the predominant clinical symptom with gynecologic findings of pelvic tumors had hystero-grams done in order to rule out an intra-uterine lesion before a conservative operative procedure was contemplated. This was of value in one instance as a submucous fibroid would otherwise have been overlooked.

Hystero-grams in three cases of post-climacteric bleeding showed a submucous fibroid in one which was treated by supravaginal hysterectomy; whereas the other two with negative hystero-grams were treated by curettage.

Finally, a patient with cervico-vaginal discharge who did not respond to the usual treatment showed on hystero-gram a uterine polyp, which was successfully treated by curettage.

The conclusions that can be drawn from an analysis of these cases emphasize the value of hystero-graphy in patients where the history, the clinical picture or the bimanual examination do not give sufficient evidence as to the exact diagnosis or indicate the method and extent of the curative procedure.

#### SUMMARY

1. Viscorayopake is a superior contrast medium for hystero-graphy.
2. An analysis of seventy-two cases of hystero-graphy is presented.
3. Excluding seven sterility patients, the remaining sixty-five cases gave positive hystero-graph findings in 24 instances, or 43 per cent.
4. In sterility, hysterosalpingo-graphy is of aid pre-operatively to exclude intra-uterine pathology. The Rubin test is of greater value in recognizing tubal dysfunction due to intra- or extra-tubal pathology.
5. The use of hystero-graphy is helpful in diagnosing intra-uterine lesions and in determining the method and extent of an operative procedure.

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# BENIGN AND MALIGNANT TESTICULAR TUBULAR ADENOMA

## REPORT OF THREE CASES<sup>1</sup>

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Tubular testicular adenoma is not only one of the rarest, but also one of the most peculiar ovarian tumors. Its significance in pathology is based on the fact that it fills the gap between true hermaphroditism and ovarian tumors of male character and opens the way for the understanding of the origin of these interesting neoplasms. The following is a report of three cases belonging to this uncommon group of new growths.

### CASE REPORTS

*Case 1.* A married woman, aged 27 years, who had never menstruated, displayed female external characteristics, was subject to female sexual desire, and manifested insignificant complaints. The axillary and pubic hair were absent, the external genitalia were definitely female, though somewhat hypoplastic. She had a vagina, but no palpable uterus. A hard, round, nodular, movable tumor in the left lower abdomen was the indication for a laparotomy.

At the operation the left gonad was found to be replaced by a whitish freely movable, solid mass of about 3 inches in diameter. The right gonad was moderately enlarged, smooth and contained two pea-sized nodules. Both gonads were connected by a transverse, arched peritoneal fold which terminated in a cherry-sized nodule on each side. There was a small, but easily recognizable tubal ampulla connected with the right nodule. Both gonads were removed and an appendectomy was performed. The immediate postoperative course was favorable; but somewhat later the well-being of the patient was impaired by the occurrence of severe flushes. These subsided gradually and disappeared after several years.

*Anatomical findings.* The left gonad (fig. 1) is enlarged by a tumor mass which is yellowish and nodular on cross section. A greater part of it is solid, but it contains occasional pin-point to bean-sized cysts. One portion, at the periphery of the gonad, is dark brown and resembles atrophic testicular tissue. The right gonad shows the same brown color on cross section and contains two pea-sized nodules resembling the tumor of the left gonad.

*Microscopic findings.* The left gonad is encapsulated by connective tissue which consists of two layers and contains large vessels. The external layer is coarse and dense while the inner layer is loose. From this capsule, septa project centrally, carrying blood vessels and dividing the parenchyma into several lobules.

The structure of the parenchyma varies in different areas. One part (fig. 2) consists of tortuous cords and tubules covered by a thin *membrana propria* composed of flat cells. The tubules are lined by a single row of columnar cells; their cytoplasm is coarsely granular and stains poorly. The cell edges are ill-defined toward the lumen of the tubule. The nuclei are ovoid, basal and radially-arranged; they contain dense, evenly distributed chromatin and distinct nucleoli. The canalicular lumen is narrow.

Another area shows a well defined lobule, the canaliculi of which are three to four times larger than the previously described average-sized tubules. Most of the cytoplasm of these cells is arranged basally being spread out in a fibrillar manner towards the lumen. Proto-

<sup>1</sup> The clinical report of the first two cases was published in the Am. J. Obst. & Gynec. Therefore only a short abstract of this report is presented in this paper in which special emphasis is laid upon the anatomic findings.

plasmic projections anastomose with one another, thus forming a loose network which fills the main part of the lumen. While the portion first described resembles the structure of an extremely underdeveloped testis, the tubules of this part have the appearance of tubules of testis after exposure to high voltage roentgen therapy. They are lined only by the characteristic Sertoli cells. Occasional tubules consist of fragmented anuclear, pale cells and are obviously necrotic.

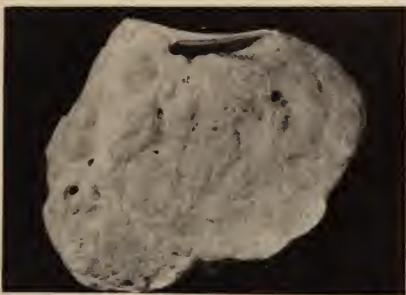


FIG. 1. Left gonad of Case 1, chiefly consisting of tumor tissue

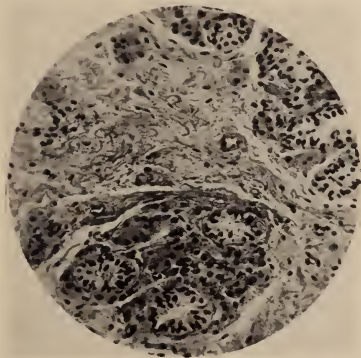


FIG. 2. Left gonad of Case 1. Area of testicular tissue consisting of underdeveloped canaliculi and of Leydig's cells.

Between the canaliculi there are numerous areas of varying size composed of closely packed polyhedral cells with round nuclei and darkly stained cytoplasm. These are arranged in sickle-shaped areas around the canaliculi and also occur without any immediate relationship to the canaliculi, in nests and cords of varying size, or as occasional isolated cells. Many of these cells are filled with brownish-yellow pigment granules. The cytoplasm is foamy and sometimes also contains large vacuoles. In Sudan III preparations most of the cells do not show distinctly stained fat granules while others show only slight diffuse orange coloration. Sickle-shaped portions at the border stain well with Sudan III.

These cells are unquestionably Leydig cells. Here and there, they form well defined darker stained nodules with many capillaries (fig. 3). These nodules resemble the well known interstitial cell adenomas which have been found in cryptorchid testicles.

Some groups of interstitial cells are found in an area of connective tissue interlaced with large vessels and nerves but free of canaliculi (fig. 4). In the section shown in figure 4, which obviously corresponds to the hilus of the gonad, the interstitial cells are in close connection with nerve bundles. They have all characteristics of the extraglandular interstitial cells or hilus cells which were described by Berger, Kohn, and others. In this case, most of these extraglandular cells contain less pigment than the intraglandular cells.

Thus, the brown portion of the gonad represents an underdeveloped testis. In contradistinction to it, the yellowish mass has an entirely different structure. It consists of extensive, straight or curved, rarely tortuous, dichotomically or even dendritically ramified cords or canaliculi. They are provided with a narrow lumen which is lined by a single

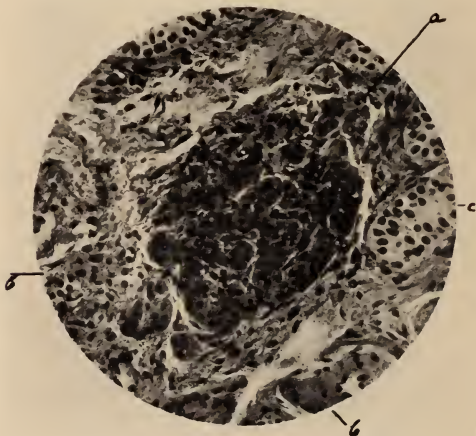


FIG. 3. Left gonad of Case 1. Leydig cell adenoma. (a) adenoma, (b) common Leydig cells, (c) testicular canaliculi.

row of fairly regular high cylindrical epithelium (fig. 5). The palisade-like arranged cells have ovoid nuclei, perpendicular to the tubule wall, being narrower, longer, and lighter stained than the nuclei in the aforementioned canaliculi. These nuclei have a fine chromatin structure and distinct nucleoli. Toward the base, the cells are well-defined, but near the lumen they are fragmented although to a lesser degree than the cells of the seminiferous tubules. There are occasional tall, slender cells with long, dark nuclei. Some portions of the lumen of the canaliculi are dilated and filled by homogeneous, well-stained, vacuolated in places collections of secretion. Where the lumen is very large, the epithelium is elevated forming simple or slightly branched papillary excrescences. Several of these cavities are large, assuming the character of cysts filled with secretion. In the larger cavities the epithelium is relatively low cuboidal, or even flat. In several places, the canaliculi are narrow and assume the form of thin, less typical cords. The tumor tubules have no real *membrana propria*; only for a short extent is such a structure discernible. There are areas in which canaliculi and solid cords form close aggregations being separated only by thin

trabeculae. In other places there are large strands of coarse, avascular, often hyalinized or even calcified connective tissue trabeculae between the tubules. There are no Leydig cells within the tumor. At the borders of the testicular tissue and tumor parenchyma there are encountered transitional stages between the two kinds of canaliculi.

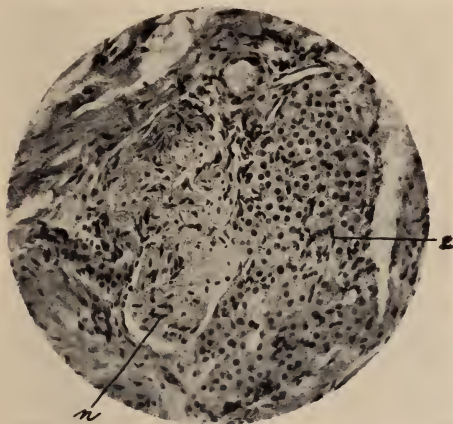


FIG. 4. Left gonad of Case 1. Hilus cells, (n) nerve, (e) extraglandular Leydig cells.



FIG. 5. Left gonad of Case 1. Testicular tubular adenoma. Hyalinized connective tissue.

Within the testicular tissue, many of the small arteries have very thick walls, which sometimes show hyaline changes. The tumor parenchyma is poorly vascularized.

Another significant feature of the left gonad is that within an extensive area of connective tissue, free of canaliculi, is the presence of several groups of closely packed tubules, the cells of which are well-defined, of low columnar or cuboidal type, containing a dark staining, small nucleus without a discernible nucleolus [fig. 6]. The lumina of these tubules are much larger than those of the seminiferous canaliculi. It is obvious that this formation differs from the testicular as well as from the adenomatous tissue. Moreover it resembles and is obviously identical with the medullary cyst structures described by Meyer, Buettner, Kohn, and others. There are no transitional stages between these tubules and the testicular and adenomatous canaliculi within the same bands of connective tissue. There are also present some narrow, dichotomically branched tubules lined with flat and at most, low cuboidal epithelium, evidently representing *rete* tubules.

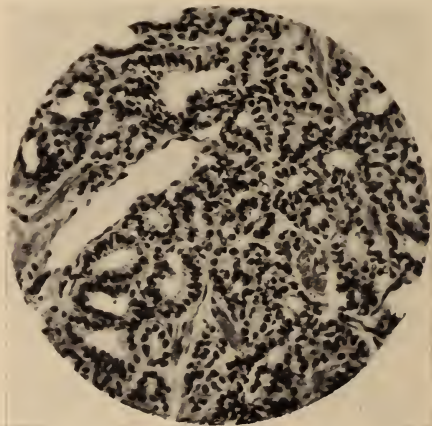


FIG. 6. Left gonad of Case 1. Medullary canaliculi in the hilus zone

The stroma of the gonad is dense in some parts, showing few nuclei and in other areas it is loose, even edematous; most of it has the appearance of ordinary connective tissue. However, several regions display isolated foci of densely arranged spindle cells resembling ordinary ovarian stroma [fig. 7]. There are isolated epithelial cords and tubules within this stroma less developed than in other places. Their nature is not clear except where definite testicular tubules reveal the true character of these epithelial formations. Some of the spindle cell tissue is more fibrillar and represents an intermediary stage between typical ovarian stroma and ordinary connective tissue.

In the vicinity of the aforementioned medullary cysts there is seen a poorly defined nodule consisting of rows of lightly stained polygonal cells, separated by loose, vascular connective tissue [fig. 8]. Here, the nuclei have a delicate structure and have a distinct nucleolus. The cytoplasm is coarse and occasionally vacuolated. The shape and arrangement of these cells somewhat resembles the adrenal cortex. It is quite obvious that this is a large accumulation of interstitial cells, although the other interstitial cells are darker and their cytoplasm is more compact and more evenly distributed. At the periphery, this formation is less distinct and projections extend into the surrounding connective tissue.

At the border of one section exhibiting testicular canaliculi, larger areas of interstitial cells, medullary tubules, spindle cell stroma, and dense connective tissue, there are well defined nests of cells resembling clusters of stratified epithelium. These are surrounded by

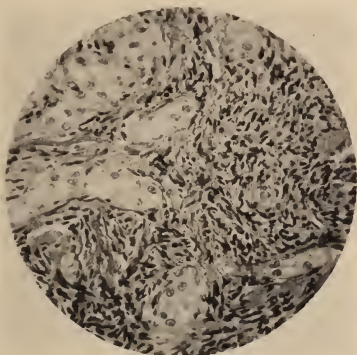


FIG. 7. Left gonad of Case 1. Ovarian stroma interspersed with testicular cords.

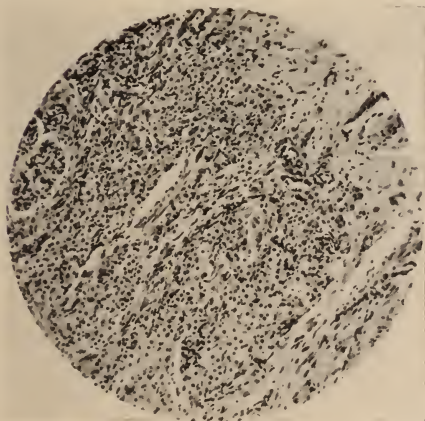


FIG. 8. Left gonad of Case 1. Area of interstitial cells resembling adrenal cortex.

dense connective tissue, displaying few nuclei and obviously represent the cell nests, generally considered to be the points of origin of Brenner tumors.

*Right gonad.* The right gonad is covered by a layer of dense connective tissue separated from the glandular parenchyma by a narrow zone of loose connective tissue. The glandular tissue has a lobular testicular structure composed of canaliculi and large areas of interstitial

cells. Here and there, the connective tissue is dense and obviously compresses the glandular tissue, so that the canaliculi are reduced to narrow cords and the interstitial cells disappear. As in the left gonad, there are some areas of spindle cell stroma. At the periphery as well as in the center of these areas, there are occasional small nests and even isolated cells, obviously rudiments of seminiferous canaliculi.

*Other parts of the internal genitalia.* The rudimentary uterus is solid and consists of smooth muscle fibers, scanty connective tissue, and blood vessels. The right tubal rudiment has the normal structure of the ampullary portion of the tube. In the left edge of the transverse peritoneal duplication, there is a structure having the appearance of a hydatid. Microscopic study reveals many vessels embedded in loose connective tissue, a few nerve fibers, considerable smooth muscle fibers, and numerous cavities of varying size, lined by a single layer of cuboidal or low columnar epithelial cells which are encapsulated by dense connective tissue containing smooth muscle fibers. The largest cavity has a lamellated connective tissue capsule, and, like the smaller cavities, contains slightly eosinophilic vacuolated material which is either granular, fibrillar, or homogeneous. Here and there, globular, owl-eyelike, vacuolated cells are interspersed between the darker columnar epithelial cells as encountered in normal tubal epithelium. In several places, the wall of the main cavity is elevated to form low simple projections.

At a short distance from the cavities, there is a nodule consisting mainly of radially arranged, large, foamy, lightly stained cells with small round nuclei. At the periphery, there are smaller, intensely eosinophilic cells distinctly demarcated from the foamy cell aggregates and are interspersed with numerous capillaries. In the vicinity of this structure which resembles adrenal cortical tissue, there is another smaller nodule consisting of the same polygonal, eosinophilic, well outlined cells seen at the periphery of the larger nodule.

*Case. 2.* A sister of the first patient, aged 22 years, had a feminine physique though she was shorter and stouter with features of a chondrodystrophic individual. She had well shaped breasts, but no axillary or pubic hair. Her external genitals were much more hypoplastic than those of her older sister. Like the latter, she had a vagina but no palpable uterus. Both gonads were substituted by ovoid, non-sensitive tumors of hen-egg to goose-egg size.

At the operation, there was the same transverse peritoneal reduplication with muscular nodules on each end and a rudimentary tube on the right side as in her sister. Some adhesions from a former bilateral herniotomy had to be dissected on operation.

For some time afterwards the patient had unusually severe and frequent flushes and sweats which continued for several years in spite of various therapeutic measures.

*Pathologic findings.* The tissue of both ovoid shaped tumors (fig. 9) is yellowish and contains many cystic cavities filled with clear colorless fluid. The right tumor is especially riddled by cavities so that the tumor tissue is reduced to the thin intervening septa. Both tumors are covered by a connective tissue capsule.

Microscopic examination of both tumors revealed identical features. The capsule consists of dense connective tissue which shows occasional small calcified areas. The tumor tissue consists of larger and smaller lobules separated by more or less thick, hyalinized, often calcified connective tissue septa. Between these septa the tissue consists of glandular tubules, simple and branched, here and there forming dense coils. The tubules consist of a single layer of high, fairly well defined, slightly eosinophilic cells which have at the base large, ovoid nuclei with fine chromatin networks and distinct nucleoli. In several places, the tubules are aggregated as large entangled heaps of cells which are separated by strands of connective tissue. In other places, there are single tubules or cords scattered in the connective tissue. Hyalin rings and loops are also noted in some areas; they resemble the well known hyaline membranes (Slaviansky loops) of the ovary.

As a rule, the connective tissue is of the ordinary type of interstitial tissue with a marked tendency toward hyalinization and calcification, but here and there it contains areas crowded with closely packed spindle cells bearing striking resemblance to ovarian stroma. Within this spindle cell tissue there are isolated tubules representing seminiferous cana-

liculi, but they are fewer and not as well developed as in the first case. Leydig cells could not be found.

In frozen sections stained for fat, there are numerous canaliculi, the cells of which contain diffuse or fine fat droplets. In the adjoining connective tissue there is encountered an isolated cell with a dark nucleus, which is filled with small and large fat droplets. These evidently represent histiocytes carrying fat from the degenerated cell material.

The cavities within the tumor are filled with a vacuolated or homogeneous material which is stained pink by eosin. These cysts are lined by a single layer of low cuboidal cells which form low papillary projections in various areas or extend into the connective tissue capsule as short glandular tubules. In several places, small areas of tumor tissue show all stages of transition from tubules with characteristic lightly stained tall cells and a well defined lumen, through narrow tubules with shorter darkly-stained cells, to the low cellular layer lining the large cavities. There are occasional groups of cells loaded with brown pigment in the neighborhood of the cystic cavities. There is no doubt that the cavities originate from the destruction of tumor tissue. The great tendency of the connective tissue toward hyalinization, calcification, and obliteration of blood vessels easily explains the consequent degenerative changes in the parenchyma of the tumor.

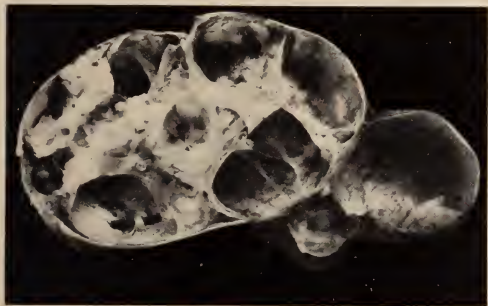


FIG. 9. Right gonad of Case 2, containing many cystic cavities

*Comment.* The similarity of the clinical and pathological features of the two sisters was obvious: both had a feminine physique, lack of axillary and pubic hair, hypoplastic external genitals and vagina, defect of the uterus and substitution of the gonads by structures of male character, chiefly by a testicular tubular adenoma; smaller areas consisted of underdeveloped testicular tissue and still smaller ones of ovarian stroma. After the removal of the tumors, both sisters, but particularly the younger one, had severe deficiency symptoms as is commonly encountered after bilateral oophorectomy.

The differences between the two sisters were slight. The older sister was good-looking and of normal stature; the younger was short, stout, and muscular. The older one had a marked libido, the younger was frigid.

An investigation of the hereditary conditions of these two sisters revealed that there were several cases of primary amenorrhea in the family and that most of their relatives had more or less marked deviations in their secondary sexual characteristics. The abnormalities were apparently transmitted from one

grandmother to her children and grandchildren. An aunt of the sisters had the same defective secondary sexual characteristics and presented the same gynecologic findings. During a herniotomy performed on her years ago an inguinally located gonad consisting of testicular tissue was removed.

Consideration of the problems arising in these two cases will follow the report of a third case belonging to this group of tumors.

*Case 3.* The third case was first seen by me in February 1934, and concerns a woman, aged 51 years, who had noted the enlargement of her abdomen and the appearance of a mass in the umbilical region three months earlier. She began to menstruate at the age of 13 and was regular. At the age of 17, she delivered a full-term baby; at 23 years, she was operated on for an ectopic pregnancy. At 37, her menses became irregular. One year later she began to suffer from profuse menstrual flow, said to have been caused by fibroids and adnexal tumors. She was given radiotherapy, resulting in complete amenorrhea. A cholecystectomy was performed in 1930. The patient had marked ascites and exhibited a blood-red translucent tumor in the umbilical region. A papillary mass was palpable in the pouch of Douglas.

At the operation on February 17, 1934, a large amount of intensely bloody ascitic fluid was emptied. The parietal and visceral peritoneum was studded with innumerable, soft, gelatinous, blood-red metastases. A large metastatic lesion was found at the umbilicus. The left adnexa were represented by a large tumor mass. The right adnexa were absent. The left adnexa and the umbilic metastatic tumor were removed. The peritoneal metastases, which bled at the slightest touch, could be easily wiped off with the hand or sponge. Because of diffuse capillary bleeding drainage was performed. The postoperative course was stormy, but led to gradual recovery. High voltage roentgen therapy was given.

After three years of good health, on about May 31, 1937, the patient again noted enlargement of the abdomen, associated with fatigue, anorexia, nausea and vomiting. She became pale and cyanotic. Marked ascites was present, and the blood picture revealed a moderate secondary anemia. There were numerous platelets. The blood calcium was 10.2 mg. per cent.

Abdominal paracentesis yielded 5 liters of intensely bloody ascitic fluid. An indistinct mass over the uterus was palpable. The patient's condition became critical after paracentesis, most likely due to intraperitoneal hemorrhage, and a diffuse ecchymosis spread from the site of the abdominal puncture, extending from the left costal arch to the left thigh (fig. 10). The patient showed a very severe anemia, with a normal platelet count, normal blood calcium and a negative Rumpel-Leede test. Blood transfusion was followed by gradual recovery and continued after high voltage roentgen therapy but lasted only a short time. The ascites recurred, her general condition steadily grew worse, and she died suddenly on November 14, 1937, probably from an abdominal hemorrhage. No post-mortem study was possible.

*Pathologic findings: Primary tumor.*

The capsule of the tumor consists of a dense outer spindle cell layer, obviously representing rests of ovarian stroma, and an inner layer of loose, delicate connective tissue with numerous, thin walled blood and lymph vessels. Several lymphatics contain tumor cells. A cap of tumor cells on the external surface of the capsule indicates that the tumor has passed beyond the capsule. Septa arising from the capsule divide the parenchyma into several areas. There are numerous large strands in which the connective tissue consists only of star-shaped immature cells, the projections of which form an extremely fine reticular network with coagulated transudate in its meshes.

The essential tumor parenchyma (fig. 11) consists of tortuous, often bifurcated, cylindrical cords with short coils and loops separated only by loose connective tissue. A true *tunica propria* is lacking, although occasional thin connective tissue lamellae accompany the epithelial cords for a short distance. A lumen is not demonstrable in the cords, but

varying sizes of small apertures disclose the tendency toward tubule formation. Some of the cords are radially arranged around large, thin walled vessels somewhat resembling liver lobules.



FIG. 10. Case 3. Extensive bloody suffusion of the skin after paracentesis.

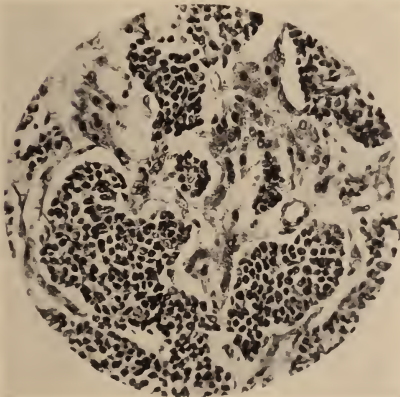


FIG. 11. Case 3. Carcinomatous testicular tubular adenoma

The individual tumor cells are polygonal, have a scanty cytoplasm and dark stained, chromatin-rich, ovoid or irregular angular nuclei most of which show no nucleoli. Many mitoses are present suggesting rapid growth.

Between the cords, there are varying sized groups of polyhedral cells with foamy cytoplasm and round light-staining nuclei, each having a distinct chromatin structure and one or two nucleoli. These cells are easily recognized as interstitial cells.

Generally, the tumor has an organoid structure, but in the areas where the structure is

particularly loose and edematous, the tumor tissue is limited to very thin, anastomosing cell strands with the cells resembling the cells of the larger, cylindrical cords. In some portions the meshes of the reticular tissue are expanded into larger cavities filled with a fine coagulated material and lined by a thin layer of tumor cells. Parts of this inner lining are elevated to form small, vascularized papillary folds covered by low cells. The extremely large number of thin walled blood vessels within the tumor are prominent and their rupture results in numerous hemorrhages.

The tumor, composed of cylindric, slightly branched, cell cords closely resembles embryonal, but rather atypical testicular tissue. This impression is strengthened by the presence of cell aggregates between the epithelial cords which are readily recognized as Leydig cells. In several places, the tumor loses its organoid structure and forms narrow epithelial cords common to carcinomatous tissue. The polychromatic nuclei and the frequency of mitoses indicate the high malignancy of this tumor.

#### DISCUSSION

In this report two sisters each presenting a benign and a third woman with a carcinomatous testicular tubular adenoma are described. In the first two instances the women were in their twenties and descended from a family with a high percentage of intersexual members. Both sisters looked and felt female. They had female external genitalia, a more or less normal vagina, but highly rudimentary Muellerian ducts. These were represented only by a transverse peritoneal reduplication with some uterine tissue on each end and by an insignificant tubal rudiment. The gonads contained some ovarian stroma but no follicles. The prevailing part of the gonads consisted of testicular tissue. In the first case, there were abundant underdeveloped testicular tubules and numerous Leydig cells. In both cases, the main mass of the gonads consisted of a benign testicular tubular adenoma which was predominantly compact in the first case, polycystic in the second, but otherwise of the same histologic structure.

The third case was a woman of 51 who not only looked female, but had also gone through a normal and an ectopic pregnancy. Her illness became apparent only after a bloody ascites developed as a result of innumerable peritoneal metastases. After removal of the primary tumor and some of the metastases and after a series of x-ray treatments, the patient made and retained a good recovery for three years. Shortly thereafter the bloody ascites recurred. Only a moderate improvement could be obtained by a paracentesis and another x-ray treatment. Within a short time her condition declined again and she died rather suddenly.

The testicular tubular adenoma was discovered in 1887 in the testicle by Langhans and in the ovary by Pick in 1905. Buettner in 1932, could report no more than 5 cases of the benign type and 4 cases of the carcinomatous form in otherwise female gonads. (These tumors are equally rare in the testicle.) Since that time, few other cases have been added. An accurate number cannot be determined because it is not always possible to differentiate the typical tubular adenoma from other reported and closely related tumors.

The testicular tubular adenoma belongs to a group of neoplasms which Meyer traced to the male genital primordium and therefore named it "arrhenoblastoma." It represents the typical form of these neoplasms because of its close similarity

to the normal testicular tissue while the atypical forms have only a distant resemblance to it. The very nature of the atypical form was revealed by Meyer's discovery of a very small middle group which represents an intermediate stage between the typical and atypical groups, clinically and anatomically.

Both the benign adenoma and its malignant form are distinguished by their yellow color and the resemblance of their cords and tubules to seminiferous canaliculi. Interstitial cells may be absent in the adenomatous tissue as in Cases 1 and 2 or may be present as in Case 3 and in the several cases reported by Pick, Neumann, Kleine, Miller, Krueckmann, and Weyeneth.

The distribution of interstitial cells in Case 1 is of interest. Large conglomerate foci are present between the testicular canaliculi where they vary in size up to small, well defined nodules, the so-called interstitial cell-adenomas, as they frequently have been seen in cryptorchic and atrophic testes (Priesel, Duerek, Berblinger, Kaufmann, Chevassu et al.). Most of the interstitial cells are in the canalicular zone, but there are also many such cells outside of the true testicular tissue within an area of connective tissue which contains many blood vessels and nerves, evidently corresponding to the hilus region. They are closely associated with the nerve-fibers and at some places form very large collections resembling adrenal cortex. Doubtless, these are the same cells which were described as extraglandular interstitial cells. (Berger, Kohn, Neumann, v. Winiwarter, Wallart, and others.)

The nature of these cells which are regularly present in the *rete testis* and ovary raised an active dispute which is still unsettled. Berger, Kohn, Watzka and Eichler, Brammann and Novak identify the extra- and intra-glandular interstitial cells, but Neumann, v. Winiwarter, Wallart, and Joachimovits consider them as phaeochromic sympathetic paraganglion cells. Kohn offers in support of his opinion the following observations: The tissue fixes well in any routine solution, it takes a bright stain in acid dyes, it lacks chromaffinity, there are occasionally present Reinke's crystals, pigment, lipoid, and certain structural details (intracellular accumulation of granules, the so-called *corps riziformes*, circumcellular connective tissue cuticles.)

According to Kohn, the proximity of the hilus cells to nerves, inducing Berger to name them sympathicotropic cells, is no proof of a genetic association of these cells to the sympathetic nervous system. Such a neurotropism can be found in other incretory cellular elements having no neurogenic characteristics. (Relationship of adrenal cortex to medulla; orohypophysis and epiphysis to the central nervous system; Masson's argentaffine cells of the intestinal tract to nerve fibers; Campenhout's sympathico-insular complex in the fetal pancreas.) The fact that characteristic hilus cells as well as true chromaffine elements are present in the hilus of the normal gonad, renders any agreement between the two opinions difficult.

Should the hilus cells of the ovary prove to be chromaffine elements they would have no particular interest, belonging to a widespread type of cells. But if they were true testicular Leydig cells, they would represent male heterosexual elements in the ovary and justify the assumption that the central part of the ovary

has testicular structure. They may also participate in the production of male sex hormone in the female. The fact that interstitial cells were found in several cases (Pick, Neumann, Kleine, and others) within the adenoma seemed to speak for the testicular character of the adenomatous tubules suggesting their origin from seminiferous canaliculi. However, since true interstitial cells are regularly present within the hilus of the ovary, their appearance in an ovarian tumor does not prove the testicular origin of the neoplasm.

There is no doubt that in Case 3 the gonad from which the tumor originated contained ovarian tissue but no follicles and but scanty ovarian stroma in the outer layer of the capsule. The fact that this woman menstruated for a long time even after the removal of the adnexa of one side proves the ovarian character of the remaining gonad. In Cases 1 and 2 the greatest part of the gonads consisted of testicular tissue in which only relatively small islands of spindle cell stroma were scattered. Follicles were not found. The seminiferous canaliculi were particularly poorly developed within the spindle cell stroma. Without the presence of typical testicular tissue in other places they could have been hardly identified as testicular canaliculi especially since interstitial cells were absent in these areas. One has the impression that there exists some antagonism between the testicular tissue and the spindle cell stroma and that one tissue impedes the evolution of the other one.

The presence of similar spindle cell connective tissue without follicles is mentioned in the descriptions or is discernible in the illustrations of some cases in the literature. Its recognition as ovarian stroma is of great importance, since it marks the otherwise male gonad as an ovotestis. This assumption is not forced, because in the reported cases of ovotestes with or without tubular adenoma we meet all possible transitions from ovarian tissue able to function to insignificant ovarian remnants. In those cases where the ovarian parenchyma is destroyed by any cause the ovarian stroma as the most resistant part becomes the last remnant of female gonadal tissue.

Case 1 had typical medullary tubes as described by Meyer in man and by Kohn in embryonal horse ovary. There was no resemblance and no connection with the testicular adenomatous tubules. The same is true for the *rete* tubules which could be seen in the same case. Since Meyer stressed the importance of the medullary cords, the medullary and *rete* tubules, and pointed out the possibility that they may be the points of origin of ovarian tumors, more attention has been given to these rudimentary formations. We know that the *rete* tubules may hypertrophy under certain circumstances (climacterium, pregnancy, myoma, insufficient development of the ovarian anlage) even forming adenoma-like structures. But these formations do not resemble the characteristic testicular tubular adenomas.

The presence of adrenal cortex tissue in the lateral part of the peritoneal fold replacing the uterus and the broad ligament and the findings of Brenner cell nests will not be discussed here, because they are accidental findings having no immediate connection with the tubular adenoma.

Most of the reported testicular adenomas are benign. If we consider all cases probably belonging to this group, 19 are benign or at least not definitely

shown to be malignant and there are 6 cases of carcinomatous testicular tubular adenoma (4 cases of Meyer including the case of Pribatsch, 1 case of Neumann and our third case.) These figures can be given only with a certain reservation because some of the 19 cases like Kleine's second and fourth cases are suspicious of malignancy. In nine cases, the tumors masculinized the patients. But in the majority, as in our three cases, no masculinization has been seen. The same holds true in regard to all cases of carcinomatous testicular adenoma. In contrast, most atypical arrhenoblastomas had a masculinizing action whereas the tumors of the middle group also in respect to sexual characteristics take a position midway between the typical and the atypical arrhenoblastomas. In general, more highly differentiated organs would be expected to function more intensely and in a more specific way than those which are undifferentiated. Heretofore, efforts to explain these really directly opposite conditions have been unsatisfactory: They are either improbable, such as the derivation of the tubular adenomas from the hormonally functionless *rete* or unproved, such as the belief of Goldschmidt that the gonads after their change into testicles continue to produce ovarian hormones. The same unsolved problem is also met in considering those hermaphroditic individuals who look and fell quite feminine in spite of more or less well developed testicles. How far this striking discrepancy depends on the hormonal activity of the gonad or on the reactivity of the soma is also unknown.

That the heterosexual gonads are not functionless, has been proved by the unusually severe and long lasting postoperative deficiency symptoms which occurred in our two sisters. Similar disturbances were noticed by Cadiz and Lipschuetz, Wagner, and Klaus after the removal of testicles in otherwise female individuals. Therefore, the loss of the small remnants of ovarian tissue in our cases cannot be considered responsible for the severe vasomotor and secretory disturbances. The vasomotor factor in gonadal function may not be sex-determined. Since such intensive vasomotor and secretory upsets are not seen in males after removal of the testicles, we must assume that the effect of the gonadic deficiency depends primarily on the specific reactivity of the female.

The experience that the mature testicular tubular adenomas occur in young people between twenty and thirty and the carcinomatous types in the climacteric and postclimacteric age has been confirmed in our cases.

Disagreement has arisen in the literature regarding the anlage material from which the tubular adenomas develop. Pick believes them to originate from seminiferous canaliculi and supports his assumption by the histologic picture, the proof of an immediate connection between the testicular and adenomatous tubules, and the presence of interstitial cells. The latter argument is nullified by the fact that interstitial cells are normal findings in the ovarian hilus. According to Pick, if a gonad contains a tumor originating from seminiferous canaliculi, but otherwise consists of ovarian tissue, it should be regarded as an ovotestis whose male portion became neoplastic. Consequently, he names such a neoplasm *adenoma tubulare testiculare ovotestis*.

Although this interpretation has been advocated by Schickele, Geist, and Traut, and with particular emphasis by Heesch, it is energetically opposed by

several other authors (Meyer, Kermauner, Kleine, Neumann, Popoff, Miller, Schiller). Meyer does not deny the possibility that such an adenoma may rise from the testicular part of an ovotestis; but he believes that the hilus formations which can be found in normal ovaries (medullary cords, tubules and *rete*) are sufficient to explain the histogenesis of tubular adenomas and the assumption of an ovotestis is at least needless. His opinion is shared by some other authors.

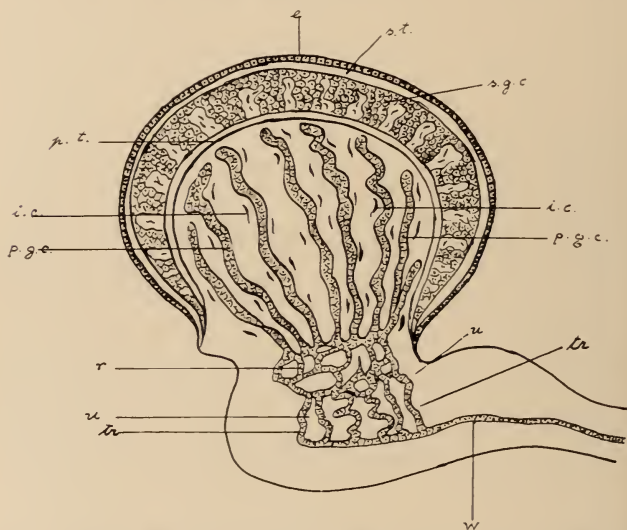


FIG. 12. Scheme of gonadal development (modified after A. Kohn): e., germinal epithelium; s.t., secondary tunica albuginea; s.g.c., secondary germinal cords (♀ ovarian cortex, ♂ additional seminiferous tubules); p.t., primary tunica albuginea; p.g.c., primary germinal cords (♀ medullary cords, ♂ seminiferous tubules); i.c., interstitial cells (♀ hilus-cells, ♂ Leydig-cells); r., rete (♀ rete ovarii, ♂ rete testis); u., urogenital junction (♀ disappears, ♂ connection between rete testis and epididymis); tr., tubules of the Wolffian body (♀ transverse tubules of the epoophoron, ♂ ductuli efferentes epididymidis); w., Wolffian duct (♀ longitudinal duct of the epoophoron, ♂ ductus epididymidis).

A short survey of the embryonal development and the architectural plan of the gonads shows this dispute to be entirely superfluous (fig. 12). In the first stage of development, the gonads of both sexes have the same architecture. In 9 mm. embryos, radiating cords of epithelioid cells suddenly develop below the coelomic epithelium of the genital fold. The characteristic testicular arrangement of these cords, the origin of which is still disputed, into germinal cords occurs in 13 mm. embryos while the differentiation of the female gonad is just perceptible in 20 mm. embryos. It is of importance that not all germinal cords develop simultaneously but by several successive stages. (v. Winiwarter

and Saimmont, Gruenwald et al.) At a later stage, the secondary germinal cords appear under the surface epithelium and push the primary cords deeper. Toward the end of the fetal life and even later, other new cords are said to develop. The testicle and ovary develop in the same direction though important differences exist in the dimensions of the primary and secondary germinal cords of either gonad. Generally we can say that in the testicle the primary, in the ovary the secondary germinal cords prevail in quantity and importance.

Most seminiferous canaliculi are formed from the primary germinal cords. The majority of the ovarian follicles arise from the secondary germinal cords while the primary germinal cords greatly diminish in the ovary, and the primitive germ cells which have immigrated into these cords degenerate. Finally, only the medullary cords remain as the remnants of the primary germinal cords. In most animals, and also in men, the medullary cords are quite insignificant structures; in several animals (fox, badger) they are conspicuous structures; in several animals (lifelong in the mole; in fetal life in the horse); they may even constitute a massive structure, a testoid (Kohn). In the female, those portions of the primary germinal cords, which are situated closer to the hilus, form the medullary tubules but may disappear without leaving a trace. In the male they form the tubuli recti. In both types of germinal glands an epithelial network originates within the gonadal blastema, the *rete*, which by means of the urogenital junction meets the neighboring tubules of the primitive kidney, the Wolffian body. While the *rete* and the urogenital junction develop further in the testicle and act as a part of the reproductive organ, these structures progressively deteriorate in the ovary. Therefore, the seminiferous tubules of the testicle correspond to the medullary cords of the ovary, the tubuli recti to the medullary tubules, and the *rete Halleri* to the *rete ovarii*. The germinal cords of the second and third proliferation form the definite follicles while in the testicle they contribute at best to a moderate increase of the seminiferous tubules.

From the standpoint of embryology, every ovary represents an incomplete ovotestis or, stressing the sterility of the central part, an ovotestoid (Kohn). "Every woman shelters within the medulla of the ovary a potential testis" (E. Novak and Long). Under pathologic conditions the medullary cords may develop further and form testicular tubules corresponding to their anlage. Since the primordial germ cells which immigrated into these germinal cords usually have degenerated, spermatogenesis does not take place. Thus no real testis, but only a sterile testoid results. If a tumor develops from the primary germinal or medullary cords, it is a typical or atypical arrhenoblastoma. Therefore, the controversy is only about words as to whether the testicular tubular adenoma comes from medullary cords or from seminiferous canaliculi. There is not the slightest essential point favoring derivation of arrhenoblastomas from medullary tubules or even from the *rete*, since the adenoma-like growths of these formations look quite different. If the ovarian tissue is gradually inhibited during the development of the neoplasm, various forms of adenomatous germinal glands result.

The cause of this change from male to female, and the growth of a tumor in

the male portion of the gonad has been satisfactorily explained by Goldschmidt's intersexuality theory, which has been successfully transferred by Krediet, Moszkowicz, and Berner to human pathology. All the cells of the organism are bisexual and contain female and male hereditary factors ( $MMFF = \varnothing$ ,  $MMF = \sigma$ ). It depends on the valence of the male and female hereditary factors, whether the individual's appearance is male or female. The greater the epistasis, i.e., the preponderance of one type of sex-determining factors over the others, the better and more marked are the characteristics of that sex and the firmer will its resistance be to all opposing tendencies meeting it in the course of life. If the epistasis is low, the first dominating sex type gradually is exhausted and at a certain moment, the "turning-point", the previously suppressed sex gains predominance. The occurrence of such a sex reversal depends on the extent of the epistasis and on other additional factors. The lower the epistasis, the earlier and the more thorough is the sex inversion. If it is very early and very thorough, a genetically female individual may develop a perfectly male appearance and vice versa (transformation man, transformation woman). If the sex reversal occurs at a later stage it can transform only that which has not yet been determined. An individual, whose development has started as one sex, but from a certain moment, the turning-point, completes it as the opposite sex, is intersexual according to Goldschmidt.

An ovotestis will develop if the turning-point falls into the evolution period of the gonad. Those portions of the gonad not yet definitely determined will develop in the direction of the new sex and the previously determined and therefore, unchangeable portions will be suppressed. As a matter of course, the turning-point provokes a great upset in the whole organism. Fallow tissue material, originally omitted from the normal development may be awakened from its rest and be induced to tumor-like growth. The origin of the arrhenoblastomas and the striking frequency of blastomas in intersexual individuals can be explained in this way.

Since intersexuality is of zygotic nature as a rule and is conditioned by coincidence of incongruent hereditary factors, it is evident that heredity plays a decisive rôle in its origin. "A female intersex comes about, if in the formula  $MMFF = \varnothing$  one or both  $M$  are too strong (or both  $F$  too weak). Thus both parents can be responsible because one originates from the father, one from the mother. If only one strong  $M$  is sufficient for the production of intersexuality, only one of the parents may be the carrier of inheritance and may himself be homozygotic or heterozygotic, all or one half of his daughters being intersexual. If both  $M$  must be strong, both parents must be carriers of inheritance for the production of intersexual daughters. In this case, both may be homo- or heterozygotic and therefore either all, a half, or a fourth of the daughters become intersexual" (Goldschmidt).<sup>2</sup>

#### SUMMARY

1. Two cases of benign testicular adenoma occurring in two sisters are reported. The gonads consisted preponderantly of testicular tissue; the ovarian

<sup>2</sup> Quoted from German original.

tissue was represented only by islands of ovarian stroma. In spite of the predominantly male character of the gonads, the individuals looked and felt perfectly feminine. Each sister had female external genitals, a vagina, but no or almost no uterus, and only a tiny tubal rudiment.

2. The removal of the malformed gonads caused severe deficiency symptoms. This was the only suggestion as to a hormonal action of these gonads.

3. In the gonads of Case 1 there were abundant interstitial cells between the canaliculi as well as in the hilus. In addition, there were medullary tubes and cell nests of Brenner character in one gonad of this case and a nodule of adrenal cortex in the broad ligament.

4. Several other members of the family were intersexual individuals.

5. A third case is reported in which a carcinomatous testicular tubular tumor occurred in a previously normal woman. In this case, as in other reported cases, no hormonal action of the tumor could be proved.

6. The gonads of these three cases are interpreted as ovotestes and the architecture of ovotestis is explained on the basis of embriologic facts.

7. Goldschmidt's intersexuality theory is applied to explain the origin of the ovotestes.

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## SYMPTOMS IN SPINAL COMPRESSION FRACTURE

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There seems to be considerable variation in the extent and severity of the symptoms following a compression fracture of the body of a vertebra. Some patients seem to be disabled for indefinite periods with pain on back motion, local pain, root pain at the level of the lesion, and even secondary so-called neuralgic or root pain distal to the lesion. On the other hand, the finding of a compression or wedging of a vertebra in a patient subjected to x-ray examination for other reasons has often shown this condition to exist without symptoms. A new chapter has been added to this study by the frequent finding of compression fractures in cases treated by metrazol shock. An unusual opportunity was offered by such cases in which it was possible to x-ray the patients before and after the metrazol convulsions, and to show that these compression fractures occurred as the result of the convulsions. A clinical history of the patient before and after the metrazol convulsion was available.

At the Hillside Hospital about forty patients who were subjected to metrazol convulsions were x-rayed by me. The findings were fairly uniform. A lateral x-ray of the dorsal spine was necessary to demonstrate the compressions. The fractures seemed to involve mainly the sixth to the tenth dorsal vertebrae. Rarely did they occur as high as the fourth dorsal, while the usual traumatic site of the first lumbar vertebra was not encountered in this series. Fractures were not demonstrated elsewhere. When this treatment is given for patients severely mentally deranged, it is impossible to follow the clinical symptoms and complaints because the patient's statements are unreliable, if obtained at all. However, the cases treated at Hillside were such that the patient's statements and observations were accurate and informative. These patients were careful observers, and were sensitive to physical stimuli and pain. The material in our forty cases was therefore more useful than the great number of institutional cases elsewhere in which the patients were unable to report even their physical complaints. Of our forty cases eight had compression fractures, mainly from the sixth to the tenth dorsal vertebrae. Of these only two showed a sharp kyphos and had local sensitiveness on pressure accompanied by mild root symptoms. The other patients were free of complaints with regard to their backs. This group represented the minimal symptoms which accompany a definite spinal compression fracture. Under normal circumstances neuroses may ensue traumatic spinal injuries. It is possible that in this group the patients had already given vent to emotional disturbances or psychoses and were relatively free of the urge to manifest signs of neurosis. I know both can exist at the same time, but I think there is something in the idea that when the patient's attention is directed to an emotional outlet he does not have to seek further psychic relief. Anyone who sees patients with back complaints is impressed by the variation of conduct and com-

plaints due to the patient's emotional reactions. Results obtained from operative procedures especially in compensation cases are thus largely influenced. A well known surgeon stated at a national meeting that he would not do nucleus pulposus ruptures on compensation cases, because the results were unfavorable. This means that the residual sensitive element can be exaggerated or depressed, and this seems to be the difference between success and failure. In other words, many of these cases retain slight sensitiveness and the patient's attitude and complaints are dominated more by psychic and extrinsic factors than the organic factor.

At the time of the discovery of these metrazol compressions, about three to four years ago, doubt was expressed as to the future course of these compressions. Bearing in mind the Kuemmell spine, which is a late aseptic necrosis and collapse in the body of a vertebra, and in which the symptoms appear late, that is, three months to two years after the accident, further trouble was looked for in these metrazol cases. I therefore x-rayed the patients in this series again and followed them for several years, and I can state that the eight cases did not show any increase in symptoms or lesion, and as far as I know, the entire group of forty cases, which have remained in contact with the Hillside management, have not brought forth complaints of back disability or disturbance. This observation is important. It bears directly on the Kuemmell spine question, which is always troublesome particularly in legal cases. Another interesting point is that none of the eight cases received any treatment or attention, and in spite of that, developed no symptoms. Of course this condition has been observed previously as an unexpected finding in patients who presented no history. Therefore it is evident that the condition can occur without symptoms. It seems that tetanus patients regularly show these lesions as may also patients suffering from other convulsive states. It is quite possible, of course, that the mechanism of this convulsive compression fracture differs from the traumatic compression fracture, which usually occurs in the lumbar region. Possibly the rib cage acts as a natural splint, and the strain is much less than that exerted in the upper lumbar region. I think compressions in the lumbar region will usually give symptoms although they may not be severe. The severe spinal fractures in which there is displacement of the vertebral column and injury to the spinal cord present, of course, entirely different pictures and should not be considered under this group for the real question under consideration here is what are the essential symptoms of a compression of a vertebral body? The older textbooks speak of all these fractures as being severe, but with the new material made available by the metrazol cases, and with the better x-ray studies many cases are found that are practically symptomless. Further observations as to probable sequelae are necessary and these cases should be followed-up over a longer period of time.

If wedge compressions occur without a history of symptoms and are disclosed by incidental x-ray examination or in metrazol cases it may be assumed that the symptoms inherent in the organic lesion are less than what can be unconsciously suppressed. So whatever they are, they are suppressable if not exaggerated, and if not suppressable they certainly are endurable.

The discovery of the existence of the necrotic intervertebral discs presented a new question with regard to the cause of the symptoms. Why should such conditions provoke symptoms while necrotic areas elsewhere may not? When adjacent tissues are involved by an inflammatory reaction the symptoms may be explained by the varying richness of the local nerve supply. This explains the extreme sensitivity of the periosteum, especially at the attachments of muscle, while many other areas in the human body are silent. Also, why should the discs give rise to backache? Involvement of the sacroiliac joint itself does not give the so-called sacroiliac syndrome. Backache most commonly is caused by sensitiveness at the lumbosacral fascia near its attachment over the sacroiliac joint. This is the area usually sensitive to pressure and on stimulation by muscle action. It explains the symptoms the patient complains of, inability to flex spine or use back—all of which are relieved by traction and rest. The complaints of patients with spinal fractures are somewhat similar; if not present immediately after injury, they certainly appear a month or two later. The diagnosis of bone disease in the sprained back rests on x-ray findings. Rarely is there a sharp kyphos or a single sensitive vertebral spine which is more than suggestive. In fact, many of the symptoms and complaints of a spinal fracture can be present in an injured back without a fracture. It is very difficult to tell clinically whether there is lack of ability to transmit force through a vertebral body, or whether the resulting sensitiveness is fascial in origin. The muscle spasm is dominant and masks the condition. In the later (chronic) stage this is still more confusing, and the picture of so-called sprained back or "traumatic spine", presents a typical pattern which borders on the neurosis, with the major factor being the mental state or personality of the patient while the underlying organic part is difficult to estimate. The symptoms when reduced to a residual pain in the back, consequent weakness and stiffness, that is restricted motility due to pain, can be overcome by patients who are willing to do so. Such patient may be rehabilitated. Those who dwell on the disability will perpetuate it. The sensitiveness certainly exists though unfortunately it cannot be measured accurately. It can be said with reasonable certainty that the remaining bone lesion is in itself not necessarily the only cause; a secondary arthritic reaction may sometimes serve as a factor.

#### CONCLUSION

Uncomplicated spinal compressions need not be the cause of fractured spine symptoms.

# INTESTINAL OBSTRUCTION RESULTING FROM MALROTATION OF THE INTESTINES. REPORT OF TWO CASES IN INFANTS\*

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Anomalies of intestinal rotation leading to obstruction of the intestinal tract have been recognized for many years. Although this condition is relatively uncommon, Gardner and Hart (4), in 1934, collected 101 cases from the literature. Few physicians have had the opportunity to observe many of these anomalies, one of the largest series being that of McIntosh and Donovan (8) of 20 cases. The outstanding contribution to the subject has been made by William E. Ladd (5) in a study of 44 cases. Ladd has not only clearly visualized the mechanics of this condition, but has shown that, by an original operative procedure, these cases can be managed successfully in a large percentage of instances. In this paper, we report two infants with intestinal obstruction resulting from malrotation of the intestines, one not operated upon, and the other treated according to the principles laid down by Ladd.

## EMBRYOLOGY

In order to understand fully the condition of malrotation of the intestines, the basic embryologic facts of the development of the intestinal tract must be outlined. Most of our present knowledge of intestinal rotation in the fetus dates back to the work of Mall (7), in 1898, and of Frazer and Robbins (3), in 1915. An important contribution was made by Dott (2), in 1923. We have drawn freely from the works of Dott and Frazer.

In the three main subdivisions of the intestinal tract, the incidence of error of development is limited almost entirely to the midgut, that portion of the alimentary canal from the duodenum to the middle of the transverse colon. The reason for this greater incidence of error in the midgut is its somewhat complicated evolution in the fetus. The midgut is divided into two parts: the prearterial portion between the duodenum and the vitelline duct (or Meckel's diverticulum), and the postarterial portion between the vitelline duct and the middle of the transverse colon.

Prior to the tenth week of embryonic life, the midgut lies outside of the walls of the abdominal cavity within an umbilical sac (fig. 1). The aperture through which the umbilical sac communicates with the abdomen is small when compared with the size of the sac and its contents. The entrance of the contents of the sac into the abdominal cavity cannot proceed, therefore, *en masse*, but must slip back in a continuous movement.

At about the tenth week of fetal life (fig. 2), the movement toward the abdomen begins with the prearterial segment of the loop. The postarterial segment is held back in the sac by the cecum which forms a mass very large in

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comparison with the size of the colon. The prearterial portion slips back in a continuous movement, its proximal portion being the first part to enter the abdomen.

As the midgut recedes into the abdomen, the coils derived from the prearterial segment, the free movement of which is permitted by their long mesentery, enter on the right side of the abdominal mesocolon and push this over toward the left. In filling the lower abdomen, due to the size of the liver in the upper abdomen, and passing to the left, the coils derived from the prearterial segment of the loop go in this direction below the continuity between the abdominal colon and that part still in the sac. The superior mesenteric artery, owing to want of growth

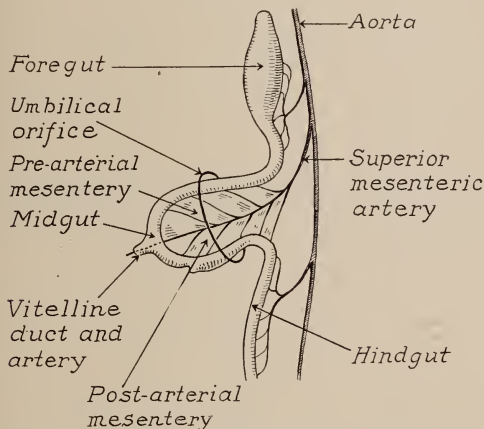


FIG. 1. Diagram representing conditions of primitive alimentary tract at fifth week of fetal life (lateral view). The foregut, midgut and hindgut are represented with blood supplies in the mesenteries. The midgut loop is large and is extended into the umbilical sac.

of the mesocolon of the sac, is necessarily with the postarterial segment in the sac, so that the mass of coils is also below this artery.

The ventralization of the prearterial segment of the loop is followed by the cecum and what is left of the postarterial segment. Since these enter the abdomen above the coils of the prearterial segment, it follows that the cecum, the appendix and the terminal ileum lie on the mass of coils of small gut. Here they are placed between the coils and the liver. As the midgut recedes into the abdominal cavity it rotates in a counterclockwise direction, and the postarterial segment (the terminal ileum, cecum, ascending colon, and the transverse colon) lies wholly on the left side of the abdomen. As this anticlockwise rotation continues, the cecum comes to lie in the superior part of the abdomen. Thus, in

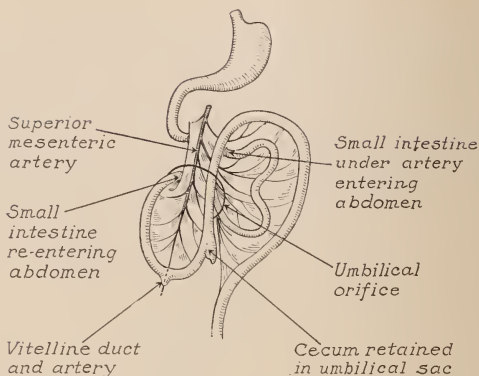


FIG. 2. Diagram representing conditions of the alimentary tract at the tenth week of fetal life (anterior view). The prearterial segment of the loop (the small intestine) has increased in length disproportionately to the postarterial segment. The small intestine is seen entering the abdomen on the right side of the superior mesenteric vessels and passing to the left side of the abdomen behind the mesenteric vessels. The cecum still lies in the sac.

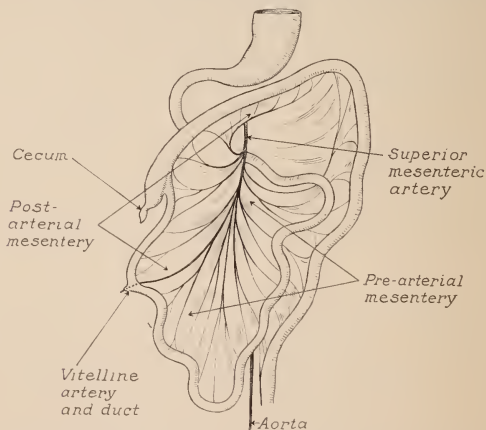


FIG. 3. Diagram illustrating conditions of the alimentary canal about the eleventh week of fetal life. The midgut loop has rotated on the axis of the superior mesenteric vessels through 270 degrees from its original sagittal plane. The cecum is now in contact with the posterior abdominal wall at the right loin. The essentials of the permanent disposition of the viscera has been attained.

the eleventh week of fetal life (fig. 3), the cecum and proximal portion of the colon lie in the epigastrium. As the rotation continues, the cecum passes into the right upper quadrant and finally ends in the right lower quadrant of the abdomen. The statement that the cecum lies at first in contact with the liver is true, but the usual assumption made from it, that the cecum descends to its final position is wrong; the liver really ascends leaving the cecum behind it (Frazer). The colon as a whole is now in its proper relation to the coils of small intestine, lying in the planes above them and on each side behind them so that this stage comes to an end, but it must be understood that although in their right planes, the intestines are in no way attached to the dorsal wall except by their median mesentery.

After rotation of the midgut is completed, there is a final stage in the development in which the cecum and ascending colon develop peritoneal attachments in the right side of the abdomen, and, the mesentery of the small intestine becomes attached to the posterior abdominal wall from the duodeno-jejunal junction obliquely downwards to the cecum.

#### PATHOLOGY

The pathologic findings in cases of malrotation of the intestines, at operation, or at post-mortem examination in fatal cases, are understood if one keeps in mind the stages of rotation of the midgut. Such abnormalities are the result of incomplete rotation of the midgut. As will be emphasized later, the true concept of the pathologic findings is not of theoretical concern, but has a very practical significance in the operative treatment of this condition.

Ladd (5) has demonstrated clearly the nature and end-results of incomplete rotation of the intestines. There are two associated abnormalities resulting from incomplete rotation of the intestines. The first anomaly is related to arrest of development of the cecum in about the eleventh week of fetal life. The cecum is arrested in the epigastrium lying below the stomach, or it lies farther to the right side under the liver. In the former location, bands of peritoneum pass from the cecum to the right postero-lateral part of the abdominal wall and these bands pass across and obstruct the descending portion of the duodenum. In the latter position, the cecum itself lies on and obstructs the duodenum. The second anomaly is related to the arrest in development of the mesentery of the small intestine. In such cases, there is a small rudimentary mesentery below the origin of the superior mesenteric artery. Such a rudimentary attachment is conducive to a volvulus of the small intestine, starting with a coil of small intestine encircling the base of the mesentery (fig. 4). The end-result of these two anomalies, is, therefore, an obstruction of the duodenum and a volvulus and infarction of the small intestine.

#### CLINICAL FEATURES

The majority of patients suffering from intestinal obstruction secondary to malrotation of the intestines are observed within the first month of life. In Ladd's series of 44 cases (5), 26 patients were seen in the first three weeks of life.

The symptoms and signs of malrotation of the intestines are related to the obstruction of the intestine. The earliest complaint is vomiting of bile-stained fluid. The obstruction is usually incomplete in the beginning so that stool is passed per rectum. Abdominal distension is a constant finding on examination. At first this is limited to the epigastrium and left upper quadrant since only the stomach and the first portion of the duodenum are dilated. As the lesion progresses the abdominal distension becomes more marked, and with advanced volvulus of the intestine, the distension becomes generalized. As the clinical features advance, the usual changes secondary to intestinal obstruction are noted: dehydration with changes in blood concentration and urinary output, and fever.

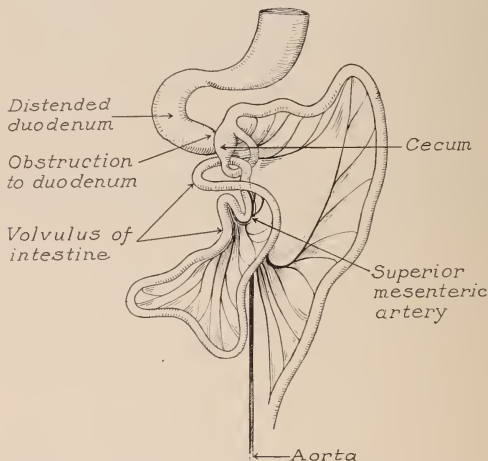


FIG. 4. Volvulus of the small intestine secondary to malrotation. The twist involves one complete turn from the original sagittal plane in a clockwise direction. The cecum lies in the epigastrium.

With infarction of the small intestine, these changes become more marked, and finally, the picture of shock and/or peritonitis is present.

Roentgenologic examination of the abdomen is of great aid in diagnosis but in this condition as in other forms of acute intestinal obstruction, barium should not be administered. Films of the abdomen, without the use of contrast media, are often very informative. In the early stages, a dilated and gas-filled stomach and first portion of the duodenum are seen, and in the later stages, marked distension of the small intestine.

#### TREATMENT

Operation must be performed in cases of intestinal obstruction secondary to malrotation of the intestines. This, however, must be supplemented by ade-

quate pre- and postoperative management (1). As a preoperative measure, which should be continued during and after operation, the administration of parenteral fluids is of the greatest importance. The fluid intake should be maintained at about two ounces per pound of body weight per 24 hours. This should be increased to compensate for loss of body fluids by vomiting or gastric siphonage. Fluids are best administered continuously by the intravenous route. A mixture of two-thirds 5 per cent glucose in distilled water and one-third normal saline is advised in infants. Normal saline may be given by hypodermoclysis when there is difficulty with the administration of intravenous fluids. If anemia or shock is present, a transfusion of blood from a suitable donor is given, and this should be repeated if necessary. A Levin tube is passed into the stomach and gastric siphonage is maintained as long as intestinal or biliary drainage continues. All of the above measures should be employed within a short period of operation to render the patient fit for surgery.

The main features of the operative technique (Ladd) will be discussed briefly. The anesthetic of choice is ether. A liberal right rectus incision is advised. After opening the abdominal cavity, it is necessary usually to exteriorize the loops of small intestine in order to visualize adequately the nature of the pathologic process. The cecum is found in the epigastrium or right upper quadrant, with obstruction of the duodenum either by bands or by the cecum itself. The posterior parietal peritoneum is incised just to the right of the cecum, in this way exposing the descending portion of the duodenum. The cecum is displaced still further to the left side, thus relieving all obstruction of the duodenum. The duodeno-jejunal junction must now be visualized to expose the rudimentary mesentery of the small intestine below the origin of the superior mesenteric artery in order to determine the presence or absence of an associated volvulus of the small intestine. In advanced cases of volvulus with infarction, the blue dilated loops of small intestine are evident immediately. If a volvulus is present, it takes place usually in a clockwise direction through one or more turns. The volvulus is reduced by turning the mass of intestines in an anticlockwise fashion. When the volvulus is reduced, the normal color of the intestines is restored unless the volvulus has passed to its final stage with necrosis of the bowel.

The postoperative management is followed according to the principles outlined above in the discussion of the preoperative treatment.

#### RESULTS OF TREATMENT

The operative mortality of cases of intestinal obstruction resulting from malrotation of the intestines was uniformly high and recovery was a rarity before the contributions of Ladd to this subject. In Ladd's group of 47 cases, treated according to the principles outlined above, there were 10 deaths, a mortality of 21.2 per cent (6). The 37 patients who survived operation have had no recurrence of the obstruction.

#### CASE REPORTS

*Case 1. History:* (Adm. 394152). N. C., a female infant, aged 2 weeks, was admitted to The Mount Sinai Hospital on June 5, 1936, with the history of vomiting nearly every

feeding since the day after birth. The vomitus was frequently projectile and bile-stained. Atropine was administered without relief. The infant had only one spontaneous stool since birth, but an enema produced several small stools. Prior to admission, the infant received 100 cc. of normal saline daily by hypodermoclyses. There were no abnormalities during pregnancy, the mother's second, or during the birth of the child. The birth weight was 6 pounds and 4 ounces.

*Examination:* The temperature was 99.6°F. and the weight 5 pounds and 10 ounces. The infant was poorly nourished and appeared dehydrated (poor skin turgor). There were no other abnormalities except on abdominal examination. The stomach outline was visible with frequent visible peristaltic waves in this region. A pyloric tumor was not palpable.

*Laboratory Data:* Blood: hemoglobin, 122 per cent; red blood cells, 5,900,000; white blood cells, 19,000, of which 60 per cent were polymorphonuclear leucocytes, and 28 per cent lymphocytes. Wassermann reaction was negative. The urine contained albumin, and on microscopic examination there were many white blood cells and occasional red blood cells (vaginal discharge present).

*Course:* The infant was placed on thick cereal feedings and atropine. A roentgenogram of the stomach after administration of barium, on the second hospital day, failed to show any evidence of an obstructing lesion at the pylorus. (The x-ray report did not give any information about the remainder of the intestinal tract.) Projectile vomiting of bile-stained fluid started on the second hospital day and continued. Atropine was stopped on the fifth hospital day. There was a bowel movement on the first hospital day, followed by a period of six days in which there were no bowel movements. On the seventh hospital day an enema was given with expulsion of a large number of pellets of fecal material and barium, followed later by a spontaneous bowel movement of yellow fecal material. Hypodermoclyses of normal saline were given at intervals. Until the seventh hospital day, the abdominal findings were essentially the same as on admission. On the eighth hospital day the infant's condition became rapidly worse. The temperature rose to 102.8°F. Cyanosis was present in addition to shallow irregular respirations. There was an icteric tinge of the sclerae. The skin turgor was poor. The abdomen became markedly distended and rigid, and the vomitus contained blood which was also passed per rectum. The child died on the eighth hospital day.

*Necropsy Findings:* The abdomen was markedly distended. The peritoneal cavity contained about 15 cc. of dark serosanguinous fluid. The loops of small intestine were markedly distended; the serosal surfaces were purplish-red in color and smooth except for scattered areas covered by fibrinous exudate (fig 5). The mesenteric root had a narrow line of attachment which extended from the duodeno-jejunal junction downward and to the right for a distance of 2 cm. The mesentery was indurated. The mesenteric veins were dilated. The mesentery of the small intestine was twisted clockwise around its axis for 360 degrees.

The cecum and ascending colon were not in their normal positions. The transverse colon, to the right of the midline, described an acute angle. Tracing this proximally, the ascending colon ran upward and parallel to the transverse colon, gradually twisting to bring its posterior surface anteriorly, and at the cecum it took another turn to the right: There was a lack of normal fixation of the cecum and ascending colon, these structures possessing a mesentery in common with that of the small intestine. The colon was contracted and pale in contrast to the infarcted small intestine. The sigmoid colon was redundant with an unusually long mesentery. The esophagus, stomach and duodenum were moderately distended.

The culture of the peritoneal fluid yielded *B. coli*.

The other abnormal findings were fatty infiltrations of the liver cells on microscopic examination, and a patent foramen ovale and ductus arteriosus.

*Case 2. History:* (Adm. 48848). R. R., a female infant, aged 1 week, was admitted to The Mount Sinai Hospital on April 24, 1942, with the history of jaundice and vomiting.

The infant was born 3 weeks prematurely. There were no abnormalities during pregnancy, the mother's first, or during the birth of the child. The birth weight was 5 pounds and 4 ounces. On the third day of life a slightly icteric tinge of the skin was noted. The infant took nourishment well and by the sixth day of life had gained 6 ounces over her birth weight. About 24 hours before admission the infant began to vomit bile-stained fluid and there was a slight rise in temperature. The vomiting continued and despite two hypodermoclyses, the infant rapidly lost weight. The bowels moved normally, but the stools were small in amount.

*Examination:* The temperature was 100.4°F. and the weight 5 pounds and 2 ounces. The infant was well developed and fairly well nourished with a bronze-like jaundice. There was a slight icterus of the sclerae. The general physical examination, including the abdomen, was negative.

*Laboratory Data:* Blood: hemoglobin, 80 per cent; red blood cells 3,700,000; white blood cells, 13,400, of which 53 per cent were polymorphonuclear leucocytes and 29 per cent lymphocytes. Icteric index, 70; urea nitrogen, 22 mg. per cent; cholesterol, 230 mg. per cent;

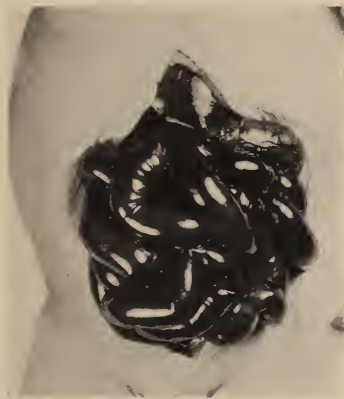


FIG. 5. Appearance of viscera on opening peritoneum at autopsy. Infarcted obstructed loops of small intestine cover the right half of the colon.

and cholesterol ester, 70 mg. per cent. The urine contained albumin and on microscopic examination showed many white blood cells.

Roentgenograms of the abdomen (without the use of a contrast medium) (fig. 6), taken on the day of admission in an interval of about 3 hours apart, revealed in one, a marked distension of the stomach with air, and in the other, a distension of the duodenum. The remainder of the intestinal tract showed only a trace of air in one intestinal loop. The appearance of the roentgenograms suggested an obstruction of the duodenum.

*Course:* The infant was observed for a period of 24 hours during which time vomiting of bile-stained fluid continued. Fluids (5 per cent dextrose in physiologic solution of sodium chloride) were given by intravenous drip continuously.

*Operation:* Operation was performed by one of us (E.E.A.) 24 hours after admission (under ether anesthesia) through a 3 inch right rectus incision. A small amount of clear fluid was present in the peritoneal cavity. The liver, gall bladder, and stomach appeared normal. The common bile duct and the first portion of the duodenum were dilated. Con-

tracted loops of small intestine filled the operative field covering the right half of the colon. There was no evident circulatory disturbance of the contracted small intestine. The small bowel was displaced to the left side and the cecum was visualized in the right upper quadrant, i.e., an incompletely rotated cecum. The mesentery of the midgut was rudimentary, about 2 cm. in length, located just below the origin of the superior mesenteric artery. The mesentery was very edematous with a coil of intestine wrapped around its base. The midgut was then delivered on to the abdominal wall, and a volvulus of 180 degrees, in a clockwise direction, was visualized. The volvulus was reduced by turning the mass of intestines in an anticlockwise direction.

Attention was now given to the other feature of the pathologic process namely, the malrotation of the colon. The descending portion of the duodenum was dilated to about 2



FIG. 6. Roentgenogram of the abdomen (without the use of a contrast medium) on admission showing dilatation of the duodenum with almost a complete absence of air in the remainder of the intestinal tract.

cm. in diameter. The obstruction of the duodenum was due to a band of peritoneal folds, running from the cecum across the descending duodenum to the right postero-lateral part of the abdominal wall. These bands were divided by incising the posterior parietal peritoneum just to the right of the cecum. This allowed exposure of the entire duodenum. The cecum was further mobilized until it was displaced toward the left side of the abdomen. At the completion of this procedure, the entire duodenum filled readily with gas, and by the time the closure of the abdomen was begun the loops of small intestine were filling with air. About 0.5 gram of sulfanilamide powder was scattered in the operative field. The abdomen was closed in layers.

*Course:* The infant withstood the operative procedure well. Fluids (5 per cent dextrose in physiologic solution of sodium chloride) were given by intravenous drip continuously

during operation and for two days after operation. The postoperative course was essentially uneventful except for a brief episode of vomiting during the second week. Roentgenogram of the abdomen (without the use of a contrast medium) at this time revealed air in many loops of small intestine and the colon with no evidence of intestinal obstruction (fig. 7). The feedings were gradually increased and the weight was 6 pounds and 10 ounces at the time of discharge from the hospital. The jaundice noted on admission subsided very rapidly and was not evident by the fifth postoperative day. The wound healed by primary union. The infant was discharged from the hospital three weeks after operation.

A follow-up examination, one year after operation, revealed the infant to be in good condition, with no recurrence of the obstructive manifestations, and weighing 25 pounds.



FIG. 7. Roentgenogram of the abdomen (without the use of a contrast medium) 2 weeks after operation showing air in many loops of small intestine and the colon (a normal x-ray in infants).

#### COMMENT

The purpose of this paper is to illustrate, by way of two case reports, the differences in management of cases of malrotation of the intestines with intestinal obstruction since the contribution of Ladd to the operative treatment of this condition. The first case illustrates the clinical course of an infant who was not treated by operation. Although a duodenal obstruction was present since birth, the infant lived for three weeks, the cause of death being the volvulus of the small intestines. It is reasonable to assume that the volvulus occurred during the last 24 hours of life. This does not mean that operation can be postponed once the diagnosis of duodenal obstruction is made, since the associated volvulus of the small intestine may occur, coincident with, or soon after the manifestations of duodenal obstruction. Even without the complication of volvulus of the small

intestines, the duodenal obstruction, in itself, will lead to a fatal outcome. The second case illustrates the clinical course of an infant who was operated upon according to the principles laid down by Ladd. An unusual feature of this case was the presence of icterus. This was undoubtedly related to the duodenal obstruction, as proven by the operative finding of dilatation of the common bile duct, and the prompt subsidence of the jaundice after operation.

#### SUMMARY

The embryologic, pathologic, and clinical features, and the treatment of intestinal obstruction resulting from malrotation of the intestines are reviewed.

Two cases of this condition occurring in infants are reported. One terminated in death, without surgery; the other treated by the Ladd operation, recovered.

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## OBLITERATION OF A CHRONIC EMPYEMA CAVITY WITH THE AID OF A FREE FAT TRANSPLANT\*

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[New York]

In 1937, Harold Neuhoﬀ ﬁrst described the use of a free fat graft for the closure of bronchopulmonary cavities. Although the procedure did not conform to the criteria ordinarily considered necessary for the success of a free graft, it succeeded in a large percentage of cases. Since the original report, this simple operation has been performed successfully in a large number of cases.

The case reported here is that of a young boy who presented the problem of a large open, chronic empyema cavity with bronchopleural fistulae. After these fistulae had been closed by pedicle muscle ﬂaps, there remained a large residual pleural space which was relatively clean but not sterile. The obliteration of such a cavity would have entailed a most extensive removal of ribs and thickened parietal pleura. This would have necessitated numerous operations over an extended period of time. As is well known, complete healing might not have been achieved.

The success obtained with free fat grafts in the closure of pulmonary cavities suggested that the same procedure might be attempted for the closure of the empyema cavity. This was done, and, although part of the graft became necrotic and was extruded, the majority of it remained *in situ*, and complete healing of the empyema cavity occurred. Such a train of events has also been observed when fat has been transplanted into bronchopulmonary cavities.

Fat has been used in many types of surgical procedures where a medium for ﬁlling residual spaces was required. In order to insure success, absolute sterility, as well as a good blood supply is essential. In both pulmonary and pleural cavities, however, neither of these conditions is present. As Dr. Neuhoﬀ stated in his original report, the procedure is entirely illogical and was performed empirically. Nevertheless, the high percentage of good results obtained in pulmonary cavities has proven its value.

The reason for the persistence of the pulmonary cavity in lattice lung is the patent bronchial fistula. The exact mechanism by which the fat aids in the closure of the fistula is not definitely known. In the great majority of chronic empyemas, a bronchial fistula can usually be demonstrated as the etiology for the chronicity. In the case reported here, the bronchial fistulae were closed by means of muscle ﬂaps before a free fat graft was considered. It is conceivable that a free fat transplant might also be successful in a chronic empyema cavity with a patent bronchial fistula.

### CASE REPORT

*History:* (Adm. 462020). A boy, aged 13½ years was admitted to The Mount Sinai Hospital on September 3, 1940, with a diagnosis of chronic empyema with bronchopleural fistulae.

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\* From the Surgical Service of Dr. Harold Neuhoﬀ, The Mount Sinai Hospital, New York.

At the age of three years the patient had pneumonia, which was followed by empyema on the right side. Thereafter, almost yearly up to the age of nine, he had recurrent empyema which required surgical drainage six different times. The last episode before entering this hospital occurred at the age of eleven and was similar to the previous ones. During the first week of August, 1940, the patient had an upper respiratory infection and remained indoors most of the time. During the next three weeks he developed a cough, elevation of temperature and dull pain over the anterior right chest. He was admitted to another hospital where a diagnosis was made of right-sided pleural effusion. X-ray examination of the chest with lipiodol instillation suggested the presence of an "abscess cavitation." His temperature ranged between 99°F. and 101°F. After one unsuccessful attempt at aspiration on August 6, 1940, an aspiration was performed ten days later yielding green pus from which streptococcus hemolyticus was cultured. Four days later, when the patient was about to be operated upon, he expectorated about six ounces of thick, green pus, and operation was deferred. Aspiration at this time revealed no pus. The patient then had a chill lasting one-half hour, but within the next few days his temperature returned to normal. On August 25, the patient again expectorated a large amount of thick pus and two days later he ruptured an empyema necessitatis through the old scar on the posterior surface of his chest wall. Because of the repeated episodes of empyema, and because of the establishment of what was thought to be a bronchopleural fistula, he was referred to The Mount Sinai Hospital for surgical treatment. There had been no history of tuberculosis, hemoptysis or night sweats. His weight had always been maintained.

*Examination:* The patient was a well developed and obese boy of 13½ years, with a Froehlich type of habitus. He appeared pale but not acutely ill. Chest examination revealed a sinus in the right lateral chest wall on a level with the seventh rib in the center of an old scar. Posteriorly, there was dullness to flatness from the fourth to the tenth rib. There was diminished tactile and vocal fremitus over the lower right chest posteriorly. There was slight limitation of motion on the right. Breath sounds were diminished over the right lower lobe posteriorly and in the axilla. Otherwise, the physical examination was negative.

*Laboratory Data:* Urine: negative. Blood: Hemoglobin, 90.5 per cent; white blood cells, 17,600; with 64 per cent polymorphonuclear leucocytes; 32 per cent lymphocytes; 4 per cent monocytes. Examination of the chest with lipiodol roentgenography revealed, "... an irregular mottled opacity in the right chest at the level of the seventh, eighth and ninth ribs. This is presumably residual lipiodol from a previous injection. Opaque material injected through a right chest sinus leads towards this opacity and also extends mesially and anteriorly, apparently just above the diaphragm. There is irregular streaked material in the right paravertebral area which appears to be present on the preliminary roentgenogram. There is an irregular cavity in the right lower chest which is probably pleural and outlined by thickened pleura. The portion of the right lung visualized and the left lung are not abnormal. There is marked scoliosis of the dorsal spine to the right in the lower dorsal area. There are old resections of the right ninth and tenth ribs, with bone regeneration."

*Operation:* On September 6, 1940, a thoracotomy with drainage of the empyema cavity was performed. Under general anesthesia, an incision was made through the old scar into the pleural cavity. This opening was then enlarged by removal of the new bone and a thickened parietal pleura. The scapula had become adherent to this new bone and had to be separated before the bony bridges could be removed. After a large opening had been made into the pleural cavity, it was found that the empyema extended to the apex of the thorax and contained numerous small pockets. A large bronchial fistula could be heard but its exact location could not be determined. Its probable site was the anterior surface of the lung near the apex. Because of the development of a rapid pulse at this time, the empyema cavity was packed with gauze, and the operation stopped.

*Postoperative Course:* The patient made an uneventful recovery, and the infection in the empyema cavity rapidly cleared up. An x-ray examination with lipiodol instillation on September 27 showed, "the empyema cavity extends posteriorly and paramediastinally

from the base at least to the level of the fourth rib. There is evidently a communication with the bronchial system because all the lower lobe bronchi are visualized. This reveals bronchiectasis of the lower lobe."

On October 8, a revision of the thoracotomy was performed in order to expose the bronchial fistula and attempt to close it. The rib above the previous thoracotomy wound was excised together with the parietal pleura beneath it. The fistula was found to lie very high up beneath the fourth or fifth ribs, and it was decided to discontinue the operation and attempt to determine the exact situation of the fistula by means of a lipiodol bronchogram in order to plan a procedure for its closure.

Lipiodol bronchography nine days later revealed that "the oil entered and outlined all the branches of the right upper lobe. There were small sacculated bronchiectases of the lower posterior branches of the lateral division of this lobe and from one of these a fistula was demonstrated entering the drained empyema cavity. The right lower lobe bronchi were drawn very close together and showed some dilatation. The lower lobe is pushed mesially and forward. The fistula is located at the level of the fifth rib posteriorly. The eighth and ninth ribs have been resected."

Because of the age of the patient it was decided to attempt to close the fistula with as little rib resection as possible. Accordingly, on September 22, 1940, the following operative procedure was performed. The incision was extended posteriorly and anteriorly around the scapula. The scapula was lifted from the chest wall and small segments of the seventh, sixth, fifth and fourth ribs were removed together with the underlying parietal pleura. The intercostal muscles were preserved and a pedicle muscle flap was formed from the muscle layer lying anterior and below the scapula. When the empyema was well opened it was found that there were numerous fistulae in an area approximately  $1\frac{1}{2}$  inches in diameter. The smaller fistulae were facing posteriorly and the largest one was presenting in an anterior direction on the lappet of the lung which was attached to the chest wall near the vertebral gutter. The three intercostal muscles were sutured into the mouths of three fistulae. The larger anterior muscle flap was then sutured over the intercostal muscles. At the completion of the insertion of the muscle flaps, no bronchial blow could be heard. The remainder of the empyema cavity was packed.

Following this procedure the bronchial fistulae remained closed and the remainder of the empyema cavity soon presented a healthy granulation tissue lining. The muscle flaps had only succeeded in obliterating the upper and anterior part of the empyema cavity and there still remained a large residual cavity posteriorly which extended to the base. Closure of this in the usual manner would have required further extensive removal of ribs and pleura. In order to avoid these radical operative procedures it was decided to attempt a fat graft which is a relatively simple procedure.

On November 12, 1940, a large segment of fat was removed from the right buttock. This was inserted into the residual empyema cavity and the soft tissues were strapped over the fat mass without inserting any sutures. The wound in the buttock was closed with silk with a rubber dam drain. The chest wound remained closed until the fourteenth day at which time a small amount of necrotic fat was extruded, followed by reclosure of the wound. The patient was discharged approximately one month after the last operation with a small granulating wound.

*Follow-up:* The granulating wound healed approximately nine months after discharge, and, at that time, the patient was symptom-free. He was seen again in March, 1943, at which time the wound was entirely healed; he had no symptoms, was attending school, had no dyspnea and felt especially well. X-ray examination at this time showed evidence of previous rib resections but the pleural cavity was entirely obliterated. There was an increase in the scoliosis which had been present before operation.

#### SUMMARY

A case is presented in which a free fat transplant was used in the obliteration of a chronic empyema cavity.

The use of free fat grafts for the closure of broncho-pulmonary and pleural cavities is discussed.

#### CONCLUSION

The successful closure of an empyema cavity by a free fat transplant suggests that it may find a field of usefulness in certain chronic empyemas whose complete obliteration is frequently fraught with great difficulties.

# WIDESPREAD CAPILLARY AND ARTERIOLAR PLATELET THROMBI

## CASE REPORT<sup>1</sup>

ALICE IDA BERNHEIM, M.D.<sup>2</sup>

[New York]

In 1936, Baehr, Klemperer and Schifrin (1) published four cases which appeared to represent a distinct clinical and pathological entity and which they called "An Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thromboses of Capillaries and Arterioles." Dr. Eli Moschcowitz (2) had previously reported a case, apparently belonging to this category, and Mark Altschule (3) has recently added another report to the literature under the title of "A Rare Type of Acute Thrombocytopenic Purpura: Widespread Formation of Platelet Thrombi in Capillaries." Since the pathogenesis of this entity is not understood and its occurrence is so rare, it is felt that the recording of another case may help toward a more general recognition of the condition and thereby aid in the elucidation of the mechanisms involved in its production. All the cases of this disease reported thus far, including the one to be detailed here, occurred in females.

## CASE REPORT

*History* (Adm. 495216). A 33 year old American housewife had been perfectly well until about two weeks prior to admission to this hospital to the Medical Service of Dr. Eli Moschcowitz. At that time radiotherapy had been applied to her hand for a dermatitis caused by adhesive tape. A few days later she noted weakness which became progressive and was followed by throbbing headache. Pallor, anorexia and ecchymoses were noted during the next few days. There was no history of drug ingestion except for an occasional aspirin.

Her previous history was negative. Her parents were both diabetics. Her father died at 71 years of age of a cerebral hemorrhage. Her brother died in this hospital of periarteritis nodosa.

*Examination.* On admission marked pallor was apparent. There were petechiae in the right aural canal, on the skin of the arms, and upper chest. Fading ecchymoses were present on the left elbow and wrist and there were several pigmented spots on the skin of the abdomen. There was a lid lag; the thyroid was slightly enlarged; a fine tremor of the hands was present. Small axillary glands were present bilaterally; no generalized lymph node enlargement was found. The liver and spleen were not palpable. The blood pressure was 110 systolic and 70 diastolic.

*Laboratory data.* Hemoglobin, 38 per cent; red blood cells, 2,000,000; white blood cells, 9,900 with 45 per cent segmented and 13 per cent non-segmented polymorphonuclear leucocytes, 1 per cent monocytes, 1 per cent basophiles, 1 per cent eosinophiles, and 29 per cent lymphocytes. Some of the latter cells may have been micromyeloblasts. There were 4 myelocytes, 3 normoblasts and 2 erythroblasts per 100 white blood cells. Platelets were markedly reduced. The tourniquet test was positive. The day after admission the sedimentation time was found to be 30 minutes; bleeding time more than 30 minutes; clotting

<sup>1</sup> This case was presented by Dr. Paul Klemperer to the New York Pathological Society, November 1942.

<sup>2</sup> From the Laboratories of The Mount Sinai Hospital, New York.

time 20 minutes. There was no clot retraction after 48 hours. That day the hemoglobin was 30 per cent; red blood cells, 1,650,000; white blood cells, 11,000 with 45 per cent segmented and 12 per cent non-segmented polymorphonuclear leucocytes, 8 per cent eosinophiles, 2 per cent basophiles, 17 per cent lymphocytes, 1 per cent monocytes, 2 per cent myeloblasts, 8 per cent myelocytes, 6 per cent reticulocytes and 5 per cent normoblasts. The blood urea nitrogen was 18 mg. per cent; sugar 90 mg. per cent; cholesterol 260 mg. per cent with esters 140 mg. per cent; icteric index 8; albumin 3.6 and globulin 2.0 Gm.; Wassermann reaction was negative. A bone marrow aspiration revealed a slightly hyperplastic marrow with a normal cell distribution. The urine showed a one plus albumin, no bile, 1:10 urobilin, 3 to 4 red blood cells and 1 to 2 white blood cells per high power field.

*Course.* Following the bone marrow aspiration, the patient went into collapse and developed signs of shock. She rallied, but a short time later again developed syncope, rapid and thready pulse, profound sweating, clammy skin and coldness of the extremities. She was given intravenous infusions and was transfused. Coma continued, however, the patient only responding to painful stimuli. She vomited several times and developed signs and symptoms suggestive of cerebral hemorrhage. Neurological examination at that time revealed diminution in response to pin prick on the left side of the body, a questionable left facial weakness and a tendency to conjugate deviation of the eyes to the right. Two hours before death, on the second day after admission, she had a tetanic convulsion. Her terminal temperature was 104°F.

In summary, this 33 year old woman was ill less than two weeks, being slightly febrile with marked anemia and thrombocytopenic purpura, dying with symptoms of cerebral involvement. The hemoglobin and red blood cells were approximately equally reduced. The tourniquet test was positive, the bleeding time greatly prolonged and clot retraction negligible, even after 48 hours. There was a slight leucocytosis and bone marrow aspiration revealed a slightly hyperplastic marrow with a normal differential cell count.

*Necropsy findings* (P.M. 12277). Gross examination performed six hours after death revealed a well developed and nourished white female with marked pallor of the skin except for the exposed parts, which were tanned. There were multiple, slightly faded ecchymoses on the extremities and abdomen and numerous petechial spots on the upper arms, chest and abdomen. The heart weighed 275 grams. The visceral and parietal pericardium as well as the myocardium and endocardium showed hemorrhagic flecking. The liver, kidneys and adrenals showed similar hemorrhagic flecking. The spleen weighed 325 grams and contained a small area of infarction. The uterus was somewhat enlarged and the endometrial surface was dark red and filled with clotted blood. The mucosa of the stomach and large bowel was markedly congested. The mesenteric lymph nodes were slightly enlarged. The vertebral bone showed normal trabeculation and bright red marrow. The thyroid gland was not obtained. The brain, examined by Dr. Joseph H. Globus, showed a few areas of reddish discoloration, particularly in the right anterior quadrigeminate body.

Microscopic examination confirmed the gross findings. In addition to the extravasations of blood, numerous capillary thrombi were found in all of the viscera except the sections of the uterus. In the hematoxylin and eosin stain, many capillaries were seen to be distended and filled or partly filled with eosinophilic, granular masses which included an occasional mononuclear cell and sporadic leucocytes. Morphologically, these were platelet thrombi with a small admixture of fibrin (fig. 1). In the heart, liver, kidneys, spleen, lymph nodes and bone marrow these thrombi were also found in arterioles. None were observed in veins or lymphatics. The age of the thrombi varied; some were apparently fresh precipitations of platelets, others older, with varying amounts of fibrin and endothelial reaction. The vessels without thrombi showed no evidence of endothelial changes, and some of the capillaries and arterioles containing thrombi likewise showed no histologically recognizable endothelial abnormalities. Peri-venous extravasations of red blood cells were observed, especially in the heart. The spleen showed small areas of fibrosis, irregular in outline, evidently healing infarcts, and one larger vessel showed an organizing thrombus. The organ was congested and contained some iron. The lungs showed a large number of megakaryo-

cytes, some within capillaries. Occasional ones showed a considerable amount of basophilic cytoplasm. The bone marrow was rather hyperplastic. It seemed normal in respect to the ratio of the individual constituents. The brain showed many areas of ischemic necrosis and numerous platelet thrombi in the cortex.

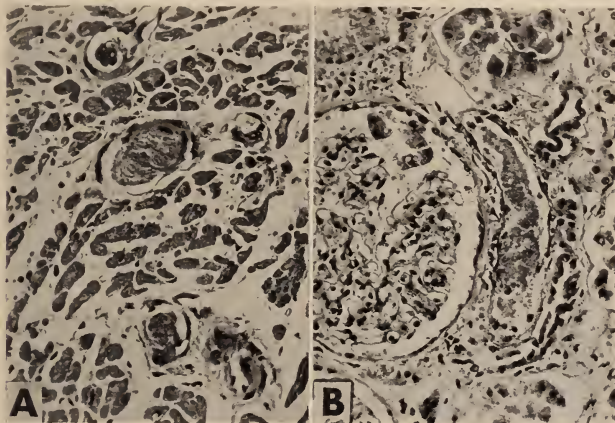


FIG. 1. (A) Multiple thrombi in capillaries of heart muscle. (B) Thrombus in vessel in kidney. Central portion shows a conglomerate mass. At the periphery individual platelets can be seen.

#### DISCUSSION

This case belongs to the group of cases showing an acute, thrombocytopenic, febrile anemia and diffuse platelet thrombosis at autopsy, as described by Baehr, Klemperer and Schiffrin (1) in 1936. The cause of the platelet thrombosis is not known. However, an analysis of the findings in this case does yield some information as to the possible mechanisms involved in the formation of the platelet thrombi.

In confirmation of the findings of the above authors, morphologic evidence of primary endothelial damage is not found. Vessels lacking thrombi do not show endothelial swelling or proliferation, and furthermore, not all of the thrombus-containing vessels show histologic evidence of endothelial reaction. This seems to indicate that the endothelial swelling and proliferation, where found, is secondary to the presence of platelet thrombi. Extravasation of red blood cells is an indication of increased endothelial permeability. However, this may also be interpreted as damage secondary to the obstruction of the capillaries and arterioles rather than a primary endothelial injury. In their original paper Baehr *et al.* (1) felt that there was no definite evidence for a primary endothelial damage. Altschule (3) more recently, on the other hand, assumes that the platelet deposition results from damage to the vascular endothelium.

What could be the mechanism by which the clots are formed in the absence of a primary endothelial damage? Normal platelets by themselves will not precipitate and form thrombi. Is there any evidence that the cause of the thromboses lies in the blood itself? That this group of patients is suffering from an obscure infection, cannot be ruled out. It is well known that blood clots more easily in infections. However, this is due to increased fibrinogen and there is no microscopic evidence in these cases, of increase of fibrin in the clots. Furthermore, the globulin content of the blood in this case was essentially normal. However, the blood albumin was somewhat lowered. The causes for a lowered blood albumin may be legion and it is useless to speculate upon them here. It may be mentioned, however, that the activity of thrombin is normally inhibited and intravascular clotting prevented by antithrombin, an as yet unidentified component of the albumin fraction of the serum (4) and further studies along this line may be indicated.

The finding of a large number of megakaryocytes in the lungs is of interest, especially in view of the physiologic evidence of loss of prothrombin in the lungs (Andrus *et al.* (5)) and in view of the suggestive experimental evidence of platelet formation in the lungs (Howell *et al.* (6)).

In their original report of cases which are similar to this one, Baehr *et al.* (1) suggested that the enormous number of platelets caught in the thrombosed capillaries in all the viscera were quite sufficient to have exhausted the available supply, and in this manner to have been responsible for the peripheral thrombocytopenia. Ordinary intravascular clots are formed largely of fibrin enmeshing a few platelets and blood cells. In the thrombi in this case, however, the platelets predominate. The question naturally arises whether clotting has taken place by the usual mechanism involving platelet disintegration and conversion of prothrombin to thrombin in the presence of thrombokinase and ionized calcium, or whether the prothrombin has been converted to thrombin by some other mechanism. It has been shown experimentally that the thrombokinase and ionized calcium can be replaced in the clotting scheme by various proteolytic enzymes derived from bacteria, and various snake venoms (7). The presence in this case and in the other reported cases of fever, a slight leucocytosis and other clinical features suggestive of an obscure infection, seems to make the action of such a mechanism worthy of future investigation. In suspected or proven antemortem cases, studies on the individual steps in the blood clotting mechanism may be of value. These are research problems, not for the usual routine laboratory.

An understanding of platelet physiology may yield information applicable to the interpretation of this group of cases. At the suggestion of Dr. Klemperer, post-mortem studies were carried out in this case, by Dr. D. Stats, to ascertain whether the blood serum of the patient contained agglutinins for platelets of the same blood group. None, however, were found.

A further point of interest in those cases is the observation that autopsy shows little evidence of necrosis despite the extent of the thromboses. This was previously pointed out by Baehr *et al.* and also by Altschule. In this case,

definite areas of ischemic necrosis were found in the brain, undoubtedly accounting for the cerebral symptoms and the death of the patient. In several of the reported cases, the cerebral symptoms suggested similar involvement. In the internal viscera most of the involved vessels were not completely occluded and furthermore, the complete capillary bed in a given area did not seem to be involved. This would seem to account for the lack of significant necrosis since evidence of collateral circulation is not apparent. Retrograde venous circulation, however, (Cohnheim (8)) cannot be excluded.

Although the reported cases are few, it is significant that to date, all the reported instances of this disease have occurred in women.

This patient's brother died with periarteritis nodosa. The familial association of a disease manifested by diffuse vascular damage, as in this case, should be kept in mind in the future.

If the clinician is aware of this disease entity, the diagnosis can, perhaps, be made during life. Because of the widespread presence of the thrombotic lesions, biopsy might establish the diagnosis.

#### SUMMARY

A case of a thirty-three year old woman with acute, thrombocytopenic, febrile anemia and post-mortem findings of generalized capillary and arteriolar platelet thromboses is described. The cause of the thromboses is unknown. Evidence is adduced which indicates that in the study of future cases attention should be directed toward abnormalities of the blood clotting mechanism. The blood serum of this patient was tested for agglutinins for platelets of the same blood group, but none were found.

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# INTESTINAL OBSTRUCTION IN A CASE OF ENDOMETRIOSIS\*

## UNUSUAL COMPLICATIONS

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The most common extraabdominal site for endometriosis is the recto-vaginal septum (1, 2). The lesion, if untreated, is prone to extend to the adjacent bowel (sigmoid and rectum) where continued progression may produce symptoms of intestinal obstruction in a manner similar to a carcinoma in the same location (1, 3, 4). Treatment may be threefold, namely: surgery, x-ray, radium, or any combination. Excision of the lesion is preferable in the younger age groups if feasible; cessation of activity in the lesion with gradual cure results from castration, either radio-therapeutic or surgical (5), although some reports show that regression does not invariably follow cessation of ovarian function (6, 7). Direct application of radium has been employed in order to obtain a shrinkage in size and relief of local symptoms (8) and also jointly with one of the other modalities.

The following case is presented because of the sequelae of an accredited course of therapy.

### CASE REPORT

*History:* (Adm. 500168) Mrs. E. G. was admitted to The Mount Sinai Hospital on January 8, 1943. The following history was obtained from her physician.

The patient was delivered in 1939 with low forceps after outlet impaction; uneventful postpartum course. The patient returned to her physician in June, 1942 complaining of lower abdominal pain of three weeks' duration, and staining. Examination revealed a bluish mulberry growth of hickory nut size in the posterior vaginal fornix; the recto-vaginal septum was thickened. The diagnosis was endometriosis of the recto-vaginal septum. A consultant believed that radiotherapy was advisable, fearing that surgery might lead to a recto-vaginal fistula. Curettage was performed; under sodium pentothal anesthesia pelvic endometriosis was palpated in the cul-de-sac. The biopsy specimen was reported as endometriosis. Local radium irradiation (radon needles, etc.) was employed under expert supervision. Moderate proctitis resulted but the lesion decreased in size. In September 1942, the disease persisted anterior and lateral to the rectum. X-ray castration was then instituted. Menopausal symptoms occurred in a month; stilbestrol was prescribed. In December 1942 discomfort and marked constipation were noted as a result of stricture of the rectum. Irregular scarring of the posterior vaginal septum was seen, and an annular tumor of the rectum whose lumen was narrower than a lead pencil was disclosed. Temporary colostomy was advised after two negative biopsies. A difference of opinion existed as to the nature of the obstruction; one thought it to be inflammatory as a result of x-ray and another thought it to be the original endometriosis in spite of the biopsies.

*Examination:* When the patient was admitted to The Mount Sinai Hospital, she was in a state of incomplete intestinal obstruction, with mild abdominal discomfort, fever (100-101°F.), rare, small thin stools, and a firm, immovable mass palpable on abdomino-vagino-rectal examination. There was a round, smooth depression just distal to the mass in the

\* From the Surgical Service of Dr. Harold Neuhof, The Mount Sinai Hospital, New York.

rectum, an ulcerated area (radiotherapy?). Barium enema revealed a two inch area of recto-sigmoid colon bearing a filling defect of irregular outline.

*Course:* The diagnosis of malignant neoplasm had to be seriously entertained because of the suggestive roentgenogram in spite of the patient's past history. During the next two days the patient had two severe rectal hemorrhages of bright blood, necessitating transfusions. On January 11, 1943 an exploratory laparotomy was performed by Dr. Harold Neuhof. A mass presented itself arising from the sub-peritoneal region of the cul-de-sac extending laterally to invade, apparently, and to surround the pelvic colon. The left ovary was imbedded in the mass. The mass was firm and the overlying peritoneum was reddened. The midline portion was entered for the purpose of obtaining a specimen; however, pus was encountered. The abscess was laid open for drainage; a gauze packing was inserted and brought out to the abdominal wall. The lower sigmoid proximal to the obstructed bowel was then drawn out of the wound, its mesosigmoid pierced with a glass rod, and the remainder of the abdominal wall was closed. On the second postoperative day the bowel was opened by cautery. The colostomy functioned well. The patient received another transfusion, chemotherapy for postoperative catheter-cystitis, and then ran an uneventful course. The sinus tract leading from the abscess gradually closed down. In the immediate postoperative period, a small recto-vaginal fistula was noted for the first time, in spite of divergence of the fecal stream. One month postoperatively the mass felt on bi-manual examination no longer was fixed. It became movable, softer, smaller and ballotable. Barium enema no longer revealed any obstruction or filling defect and the bowel margins were less rigid. The recto-vaginal fistula was still present. Three months postoperatively the mass had practically disappeared. The pelvis was no longer "frozen" but free. The recto-vaginal defect was so small that it could not be definitely visualized. The patient will be permitted to carry the colostomy until the pelvic mass disappears and the recto-vaginal fistula closes; it will then be closed.

#### SUMMARY

A case of endometriosis of small size which appeared to have been treated adequately but in which complications developed related to reaction to treatment is presented. These complications were pelvic abscess with an inflammatory reaction invading the cellular planes about the pelvic colon and producing intestinal obstruction which, because of its roentgen features, simulated carcinoma of the large bowel; hemorrhage from the large bowel due to ulceration; and recto-vaginal fistula. Drainage of the pelvic abscess, and colostomy resulted in subsidence of the clinical manifestations and progress toward cure.

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# CYSTIC LYMPHANGIOMA OF THE OMENTUM CAUSING AN ACUTE SURGICAL ABDOMEN<sup>1</sup>

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Lymphangiomata of the omentum occur with sufficient rarity as to constitute a clinical curiosity. It is difficult to evaluate the true character of the various lesions reported as "omental cysts" in the literature, but Montgomery and Wolman (7) carefully selected 53 cases of lymphangiomata from the literature to 1935, including 2 cases of their own. Although Guernsey in 1939 (3) was able to collect 15 cases from the files of the Mayo Clinic over a twenty year period, 11 of these were incidental findings at operation or autopsy, and 1 represented a foreign body pseudocyst; only 3 presented symptoms referable to the cyst as the cause for operation. Individual case reports since 1935 would contribute about 18 additional cases, although the exact number remains questionable because of gaps in the clinical or pathologic data.

By far the great majority of the cases of omental cyst were explored because of symptoms that were slow in developing, such as increasing abdominal girth, failure to gain weight, or loss of appetite. The occurrence of a case presenting acute symptoms and signs of such severity as to simulate an acute surgical abdomen is sufficiently unusual and interesting to merit reporting at this time.

## CASE REPORT

*History:* (Adm. 498851). A 10 year old white girl was admitted to the hospital on December 7, 1942, having been awakened about twelve hours before entry by severe left lower quadrant pain. The pain was cramplike, localized to and persisting in the left lower quadrant, without radiation. Following the onset of the pain the patient vomited three times, and had one formed stool which was of normal color. She had noted a thick malodorous vaginal discharge for the previous two weeks, and had a slight upper respiratory infection one week earlier. Childhood illnesses had included measles, chickenpox, and whooping cough, aside from which the child had been in good health. There was no past history of diarrhea, constipation, or bloody stools, and no antecedent trauma.

*Examination.* The girl was well developed and well nourished, complaining of abdominal pain. The temperature was 101.6°F., and the pulse rate was 140 per minute. The pharynx was not injected, and there were no abnormalities except on abdominal and rectal examination. In the left lower quadrant there was exquisite tenderness, even to superficial palpation, with marked spasm. Rebound tenderness was referred from the right lower quadrant to the left lower quadrant. The remainder of the abdomen was soft and non-tender, and the liver edge was palpated one inch below the right costal margin. On rectal examination there was definite fulness on the left side, with tenderness on both sides. A small amount of purulent material was present in the vagina. Gram stain of this material disclosed only a few gram positive cocci; culture revealed *Staphylococcus Albus* B., overgrown by *B. coli*.

There were 16,200 white blood cells in the peripheral blood, of which there were 80 per cent polymorphonuclear leucocytes and 20 per cent lymphocytes. Urinalysis revealed a concentrated urine, with a specific gravity of 1.034, containing acetone, but with no abnormal microscopic findings.

<sup>1</sup> From the Surgical Service of Dr. Ralph Colp, The Mount Sinai Hospital, New York.

An intravenous infusion of a 5 per cent dextrose solution in sodium chloride was started. The clinical impression was that the child was suffering either from a Meckel's diverticulitis, or from acute appendicitis presenting in the left lower quadrant, and that exploratory laparotomy was indicated. Other diagnoses included that of twisted ovarian cyst and hematosalpinx.

*Operation.* Operation was performed two hours after admission under drop ether anesthesia. The peritoneal cavity was entered through a 3 inch midline suprapubic incision, with the escape of a large amount of clear fluid. Deep in the left lower quadrant was seen a bluish cystic structure which could easily be delivered. This proved to be a multangulated, flattened, tense cyst, roughly the size and shape of an adult pancreas, arising from the great omentum. It had dragged the omentum low into the pelvis, and while there was no definite gross evidence of torsion of the cyst, the original blue color was rapidly replaced by a shiny yellow. There was no obvious opening in the sheer wall of the cyst, and the contents appeared gelatinous and homogeneous. The cyst was resected intact over clamps, together with a small portion of the omentum from which it arose. Exploration of the re-



Fig. 1. The irregular configuration of the cyst is clearly seen, together with the site of origin from the omentum.

mainder of the pelvis revealed the undeveloped uterus and adnexae to be free from abnormalities. A small amount of coagulum was present in the cul-de-sac. The appendix was thickened, bound to the cecum by several fairly firm adhesions, and appeared to contain several small fecoliths. With the remainder of the peritoneal cavity walled off, appendectomy was performed with ligation of the mesenteriolum and chromic ligature and carbolization of the stump. Two grams of sulfanilamide were placed over the base of the appendix. The abdomen was closed without drainage, with continuous chromic for the peritoneum, interrupted chromic for the fascia, and interrupted on-end mattress sutures of silk for the skin.

*Course.* The patient made an essentially uneventful recovery. A small hematoma appeared in the wound, which was evacuated, following which rapid healing took place.

*Surgical pathology.* The specimen consists of a portion of omental tissue and a cystic structure with an irregular contour. The omental tissue is seen to consist of yellow fat and delicate, transparent intervening tissue containing capillaries. The cystic mass measures 11.5 x 3.5 x 1 cm. in its largest diameters. It is semi-transparent, with a very fine vascular network over the entire surface. Somewhat yellow material shines through the thin sur-

face. The shape is largely elongated with two finger-like projections about 1 cm. and 6 cm. respectively in diameter (fig. 1).

Histologically the specimen does not differ remarkably from those previously described in the literature. The wall is thin and fibrous, and is lined by flattened endothelial cells. Numerous dilated, engorged capillaries are to be seen. The cyst contents take a pale, homogeneous stain. On the external surface of the cyst wall, there is a fairly marked infiltration of leucocytes, consisting of lymphocytes and polymorphonuclear cells in about equal proportions; examination of a section prepared with the Gram stain failed to disclose the presence of any bacteria.

*Diagnoses.* Cystic lymphangioma showing acute inflammation; appendix without significant changes.

#### DISCUSSION

The failure to include cystic lymphangiomata of the omentum among the potential causes for an acute surgical abdomen in the current literature is proof of the infrequency with which this actually occurs. Ladd and Gross (6), in their textbook on the Abdominal Surgery of Infancy and Childhood, mention 3 cases of omental cysts, in none of which acute symptoms were present. However Montgomery and Wolman (7), in their analysis of 53 published cases, found 6 with acute symptoms due to twist of the pedicle or rupture. All 3 of the omental cysts described in the paper by Berger and Rothenberg (1) had ruptured preoperatively, giving rise to pain, vomiting, tenderness, and rigidity. The clinical picture closely simulated that of acute appendicitis or twisted ovarian cyst. Hall (4) mentions the possibility of acute symptomatology, but the operative indication in his case as in the case described by Horgan (5) was slowly increasing abdominal distension. The youngest recorded case, reported by Eichwald (2), resulted in a fatal ileus in a female infant three weeks of age.

Although it would be tempting to try to relate the acute symptoms and signs in the present case to infection derived either from the vaginal discharge of recent onset or the upper respiratory infection present a week previously, the laboratory data make such a hypothesis untenable. No organisms were found in the free intraperitoneal fluid, and no bacterial growth was obtained on culture. Additional evidence is supplied by the lack of organisms in the fixed preparation. The available information points, therefore, to a mechanical rather than an infectious etiology to account for the inflammatory features of the case. The rapid change in color following delivery of the cyst points to a possible torsion, whereas the presence of a small amount of white coagulum in the cul-de-sac indicates that spontaneous rupture of a small portion of the cyst may have occurred.

The surgical treatment of omental cysts, whether explored because of acute or chronic symptoms, has been uniformly satisfactory. Recurrences have not been recorded, and the postoperative course has usually been smooth. Although there are no characteristic features whereby one should make the correct diagnosis pre-operatively, and although more common conditions should be kept uppermost in one's mind, the occurrence of this lesion must be considered in the differential diagnosis of the acute surgical abdomen.

## SUMMARY

A case is presented of cystic lymphangioma of the omentum causing an acute surgical abdomen.

A review of the literature discloses that the great majority of the cases of omental cyst were discovered either incidentally, or at operation because of chronic symptoms such as abdominal distension.

Nine cases were found resembling the present instance both clinically and pathologically.

The existence of this entity should be borne in mind in the differential diagnosis of the acute surgical abdomen.

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## ABRUPTIO PLACENTAE

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Obstetrical literature is at such variance regarding the etiology of *abruptio placentae*, and obstetricians disagree so markedly in the management of the condition, that the presentation of a case occurring in a healthy primigravida without toxemia, together with a discussion of its management, appears in order.

### CASE REPORT

*History:* Mrs. A. N., a 25 year old primigravida, last menstrual period May 13, 1942, was first seen on September 15, 1942. The past history was negative except for appendectomy and removal of small ovarian cyst 1 year previously.

*Examination:* There were no general physical abnormalities. The blood pressure was 122 systolic, 68 diastolic; hemoglobin 100 per cent. Urinalysis showed no albumin and no formed elements were present. The blood Wassermann reaction was negative. The uterus was enlarged to the size of a 14 weeks gravidity. The fetal movements were first felt on October 7, 1942 and the antepartum course was entirely uneventful. She gained a total of 18 pounds, the urine remained negative for albumin and the blood pressure ranged from 122 to 128 systolic and 68 to 84 diastolic during regular antepartum examinations conducted every two weeks.

*Course:* At 5:30 A.M. on January 23, 1943, approximately 4 weeks before term, the patient reported a gush of blood from the vagina together with the passage of large clots. She was immediately hospitalized and gave a history that, without antecedent exertion or trauma, at 11 P.M. January 22, 1943, she began to experience severe lower back pain, constant and increasing up to the time of admission, when she began to complain of severe constant right lower quadrant pain. On admission to the hospital the patient was anxious, pale, perspiring, and presented the picture of shock. The pulse was 106 per minute, of fair quality, the blood pressure was 108 systolic and 64 diastolic. The uterus was in tonic contraction and there was exquisite tenderness over its right lower portion, where its consistency was board-like. No fetal heart sounds could be made out and the patient had felt no fetal movements since the preceding midnight. Rectal examination showed the head just dipping into the pelvis with the cervix long, firm, and just patulous to the finger tip. There was continuous moderate vaginal bleeding. The patient was immediately typed and crossmatching was ordered, including Rh compatibility matching with donor and banked blood. An infusion of glucose in saline was started and the operating room ordered for cesarean section. In the next half hour while the operating room was being prepared, the vaginal bleeding shock and pain increased and the ligneous area in the right lower half of the uterus spread to involve the entire right half of the uterus. Because of the progressive nature of the shock, and increased bleeding, cesarean section was decided upon and this was concurred in by two obstetrical consultants.

*Operation:* Under general anesthesia the abdomen was opened and the entire right half of the uterus presented the so-called "Couvellaire" appearance of utero-placental apoplexy with extensive blood extravasation into the myometrium and subperitoneally so that it was literally "black and blue." A low flap cesarean section was quickly performed, revealing a completely separated placenta, numerous blood clots, and about 400 cc. of free blood in the uterine cavity. A 6½ pound stillborn male fetus was quickly extracted. Pituitrin and ergotrate were administered and the uterus was snugly packed with iodoform gauze. Because the uterus contracted well and there was no further bleeding, it was felt safe not to do a hysterectomy in spite of the extensive infiltration of the entire right half of the uterus.

\* Dr. Hiram N. Vineberg Research Fellow in Gynecology (1938-39).

*Postoperative Course:* The condition of the patient was good, with no further drop in blood pressure or rise in pulse rate, and transfusion was not deemed necessary. The post-operative course was uneventful. The patient's highest temperature was 100.8°F. the day after operation, when the uterine packing was removed, and she was discharged well on the twelfth day after the operation. Blood pressure was 120 systolic over 82 diastolic, and repeated urinalysis revealed no albuminuria.

#### DISCUSSION

Much has been said concerning the etiology of *abruptio placentae*—probably the final word is still to be said. 1) Trauma, by direct external violence or by traction on a short cord, has been suggested. It is admitted that this is an infrequent factor in most cases. 2) Structural or developmental defects of either the placenta or the decidua have been suggested but few specific instances have been reported in the literature. (On the contrary, adherent placenta would appear to be the more frequent occurrence in this condition.) 3) Psychoneurotic extreme emotional strain producing irregular uterine contractions has been postulated but never proved. 4) Recently a disturbance of the relationship between vitamin E and the estrogens has been emphasized, and on this basis Shute (1) has advised the use of vitamin E prophylactically. 5) Toxemia is probably the most frequently associated clinical condition predisposing to *abruptio placentae*. Of particular interest in this field are the studies of Hofbauer who, on the basis of his histamine studies, postulates a specific toxin as a causative factor. It has been pointed out that histamine injection into pregnant animals with placentae similar to humans, produces a clinical condition of shock, increased capillary permeability and fragility, diapedesis, and an oxytocic effect (although this is said to be only about  $\frac{1}{1200}$  as strong an action as that of posterior pituitary hormone). Moreover, from the viewpoint of the pathologist, the hepatic and renal changes produced by chronic histamine poisoning are very similar to those found in severe toxic hyperemesis gravidarum while acute histamine poisoning results in changes much like those found in the liver and kidney in the eclamptic group of toxemias. The basic picture of diapedesis through the walls of terminal maternal arteriolar capillaries into the substance of the decidua basalis followed by lesser or greater extravasation into the myometrium has been clearly pointed out in the toxic group of patients. 6) The unexplained group of cases with no antecedent or concomitant toxic manifestations remains a complete mystery in the present state of our knowledge and the present case without trauma or toxemia is a challenge to modern obstetrics.

The symptoms, signs and pathologic findings have been so well described that they need no emphasis. Pain may range from mild local discomfort to constant intense generalized abdominal pain. Shock is marked and out of all proportion to the amount of obvious blood loss. Uterine tenderness, local or diffuse, depending upon the extent of the lesion, is nearly always present. In the present case it was interesting to note the rapid increase of the uterine extravasation during a short period of observation.

All obstetricians agree that the mild cases with little separation and little or no shock or bleeding should be treated conservatively. They agree, too, that

*accouchement forcé*, or artificial dilatation or incision of the cervix is contraindicated. There is universal agreement, too, in all cases, regarding the need for combating shock and blood loss by prompt intravenous administration of saline, glucose, plasma, and/or blood (and in the present state of our knowledge, proper attention must be paid to Rh compatibility).

There is a wide difference of opinion, however, concerning the management of the severe group of cases. The conservative group holds that the severe cases should be managed like the mild ones, combating shock, but to utilize cesarean section only when it is specifically warranted on a mechanical basis, e.g., cephalopelvic disproportion. Many American observers, as well as two in the Dutch literature, Stroink (2) and Bastiaanse (3), stress the low mortality (less than 5 per cent) by conservative management alone.

The radical group, on the other hand, holds that the best maternal results, as well as more live babies, ensue when cesarean section is resorted to. Miller concludes "that indications for cesarean section in the treatment of premature separation of the normally implanted placenta should be extended wherever ideal conditions are obtainable."

Individualization of each case, consideration of the condition of the mother, of the maturity and condition of the fetus, dilatation of the cervix, and the facilities available, all must play a part in helping the obstetrician to make his decision.

In the present case of *abruptio placentae* the shock, bleeding, and increasing size of uterine infiltration necessitated operative intervention to terminate the pregnancy. Conservative management or delay in intervention not only would have endangered the patient's life, but also might have made subsequent hysterectomy necessary.

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# HEMATURIA COMPLICATING FIBROMYOMA OF THE UTERUS\*

SEYMOUR WIMPFHEIMER, M.D.

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Urologic complications are not uncommonly associated with gynecologic conditions. Those most frequently noted are the result of pressure on the ureter and bladder by benign or malignant pelvic tumors, or inflammatory conditions involving the uterus and adnexa with their adjacent supportive structures. Hydronephrosis secondary to uterine prolapse has been described (1). Urinary retention with resultant infection has occurred. In all these conditions it is unusual to see hematuria, unless some gross lesion is found in the urologic tract.

Therefore, the following case of hematuria complicating a large fibromyoma of the uterus merits reporting.

## CASE REPORT

*History:* (Adm. 496488). A 32 year old woman (gravida 1, para 0) was admitted to the medical service of The Mount Sinai Hospital on October 13, 1942, complaining of bloody urine of two days duration. In addition she experienced severe pain, swelling and stiffness of the right knee for one month. During the past four years, there was intermittent pain in the right loin. This pain was aggravated one month before admission, and was associated with pain in the left shoulder and left knee. These pains disappeared in one week, but the pain in the right knee persisted and was aggravated by walking. There was some frequency and nocturia 3X, but no dysuria.

The patient was married for 19 years, had one induced abortion 19 years ago. The menses began at 12, occurred every 30 days and lasted 4 to 5 days. No menstrual irregularities were noted. The last menstrual period occurred on October 7, 1942. There had been no change in weight.

*Examination:* The patient was a well developed and well nourished negress, not acutely ill. Examination of the head, neck, heart and lungs revealed no gross abnormalities. The abdomen was distended by a large irregular mass, which occupied the lower portion and extended well above the umbilicus. The mass reached almost to the costal margin on the right side, while on the left side its upper limit was on a level with the iliac crest. The gynecologic examination showed a normal vulva and vagina. The cervix appeared normal. The pelvis was filled by a hard fixed irregular nodular mass, which was continuous with the abdominal mass. The right knee was swollen, warm, but not tender. There was marked pretibial edema and limitation of motion. The blood pressure was 106 systolic and 78 diastolic.

The diagnosis on admission was: Infectious arthritis, nephritis, fibroid uterus.

*Laboratory data:* Urine: grossly bloody; specific gravity 1.010; 4 plus albumin; negative sugar and acetone; microscopically many red blood cells were seen. Blood: Hemoglobin, 62 per cent; red blood cells, 4,090,000; platelets, 280,000; white blood cells, 5,200, with 61 per cent segmented polymorphonuclear leucocytes; 6 per cent non-segmented; 19 per cent lymphocytes; 10 per cent monocytes; 3 per cent eosinophiles and 1 per cent basophiles. Bleeding time, 3 minutes; coagulation time, 10 minutes; clot retraction, present.

The hematologist's opinion was as follows: "Except for a moderate hypochromic anemia the blood picture including test for hemorrhagic diathesis is normal. There is no hematologic evidence to explain the hematuria."

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\* From the Gynecologic Service of Dr. I. C. Rubin, The Mount Sinai Hospital, New York.

X-ray examination of the abdomen showed a tissue mass arising out of the pelvis and reaching level of third lumbar vertebra. The lower dorsal spine and sacro-iliac joints showed productive osteoarthritic changes.

X-ray examination of the right knee revealed a slight degree of productive changes along the antero-superior angle of the patella. The right knee was aspirated of 50 cc. of cloudy, pale yellow straw colored fluid. Culture of the fluid was sterile and inoculation of guinea pig for tuberculosis was subsequently reported negative. The pain and swelling in the knee subsided after aspiration. The orthopedist felt that the knee condition was due to a pre-patellar bursitis.



FIG. 1. Retrograde pyelogram showing a filling defect in the right ureter at the level of the fourth lumbar vertebra

The urological tract was then investigated for the etiology of the hematuria. An intravenous pyelogram revealed no abnormality on the left side. On the right side, the calyces and pelvis were normal. The upper portion of the right ureter revealed a filling defect measuring  $1\frac{1}{2}$  inches. Above and below this defect the ureter appeared normal or slightly dilated.

Cystoscopy revealed a normal bladder mucous membrane. The ureteral orifices appeared normal. There was a protrusion of a mass into the floor of the bladder posteriorly. The trigonal region was congested. There was a bulbous edema of the sphincter, which bled readily. The cystoscopist concluded that the hematuria was due to pressure of an

extra vesicle mass resulting in vascular stasis and bleeding. However, since the intravenous pyelogram showed a filling defect in the upper portion of the right ureter, a retrograde pyelogram was done, on the right side. This showed the pelvis and calyces to fill normally. The ureter was normal down to the level of the fourth lumbar vertebra, where there was a filling defect of about one inch below which the ureter was again visualized, but seemed to be dilated (fig. 1). Because of the radiographic defect the cystoscopy was repeated. No blood was observed coming from the right ureteral orifice. The right ureter was catheterized 28 cm. without obstruction. The ureteral filling defect remained in all plates, but no definite diagnosis of ureteral tumor could be made. It was suggested



FIG. 2. Retrograde pyelogram performed after removal of the fibromyoma of the uterus. The filling defect in the right ureter is no longer present.

that the pelvic tumor should be removed, and that if the hematuria persisted, the urologic investigation be repeated.

During all this time, the patient continued to void bloody urine. The patient's condition was improved pre-operatively by a blood transfusion.

*Operation:* Laparotomy was performed on November 9, 1942, under gas, oxygen ether anesthesia. The uterus was found to be irregularly enlarged to the size of a four months gravidity. There was a subserous, almost pedunculated fibromyoma, the size of an orange, extending upward from the right side of the uterus. The intestines were densely adherent to the uterus and adnexa. The tubes and ovaries were thickened and fixed to the broad

ligament, and to the posterior aspect of the uterus. The right ureter and kidney were palpated, but no gross abnormality found.

A supravaginal hysterectomy and bilateral salpingo-oophorectomy was done. An iodoform pelvic drain was inserted through the cervix and 5 grams of sulfanilamide powder was instilled into the pelvic cavity.

*Course:* The patient's postoperative course was uneventful. The first catheterized specimen of urine eight hours after the operation was clear and contained no red blood cells. All specimens of urine thereafter were clear and contained no blood. A postoperative cystoscopy showed the ureteral orifices to be normal. Both ureters were catheterized without obstruction. Excretion of indigo carmine was normal. A right ureteropyelogram revealed that the defect seen on preoperative films was no longer present. The ureter was completely outlined in its entire course (fig. 2).

The patient's convalescence was uncomplicated. She was discharged on November 24, 1942. Subsequently, the patient was seen at the follow-up clinic on January 22, 1943. She felt well and experienced no recurrence of the hematuria.

#### COMMENT

The diagnosis was at first obscured by the association of the anemia, the joint pains and the loin pain with the hematuria. These clinical findings emphasized the possibility of a lesion in the kidney or ureter since there was no menstrual disturbance to account for the anemia. The unusual finding of an unexplained ureteral defect further complicated the clinical picture. It was only after considerable discussion that it was decided to remove the pelvic mass and repeat the urologic investigation following the operation.

Since the hematuria disappeared immediately following the removal of the uterine fibromyomata and adnexa, it is most probable that the pressure of the tumor produced vascular stasis with rupture of vesical veins resulting in bloody urine.

Cystoscopy at no time revealed any blood from the right ureter. Therefore, it is unlikely that the hematuria came from this source. The ureteral defect may have been due to direct pressure or muscle spasm, secondary to pressure of the large pelvic tumor. This defect was not visualized in the retrograde pyelogram performed after the removal of the fibromyoma of the uterus.

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## CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

*Monday, March 23, 1942*

### *Case 1. Spongioblastoma Ependymale*

*[From the Neurosurgical Service of Dr. Ira Cohen]*

*History:* (Adm. 476947; P.M. 11946). A woman, aged 59 years was apparently well until two months before entering The Mount Sinai Hospital, when she developed bilateral occipital headaches, and began to express ideas of persecution. Six weeks later her headaches became severe and were accompanied by vomiting. Shortly thereafter she developed some impairment of vision, weakness of the right side of the body and unsteadiness of gait with a tendency to fall to the right. During her last two weeks at home she became progressively more drowsy, confused, and was confined to bed. Her speech became garbled and she found it difficult to express herself. She repeatedly mentioned dreams without describing them, and spoke Norwegian, a language which she had seldom used for many years.

*Examination:* The patient was drowsy, apathetic, and disoriented. Her memory was very poor. In general her intelligence seemed to be impaired, but she was able to carry out simple commands quite well. Speech was somewhat garbled, frequently unintelligible, and there was definite anomia. Skull percussion over the left frontal area yielded a hollow note and provoked some pain. There was bilateral papilledema, more marked on the left side. The neck was moderately rigid and there was a Brudzinski sign. There was a right hemiparesis with a right central facial weakness and slight deviation of the tongue to the right. Tendon reflexes were hyperactive on the right, and there was a bilateral Babinski sign. The abdominal reflexes were absent on the right and diminished on the left. Sensory examination was uncertain because of the patient's mental condition, but there seemed to be no sensory defects. The blood pressure was 160 systolic and 80 diastolic. The heart was somewhat enlarged to the left and the pulse rate was 60.

*Laboratory Data:* Urine, negative. Blood: White blood cells 16,000 with 89 per cent polymorphonuclear leucocytes, otherwise normal. Cerebrospinal fluid: Initial pressure, 120 mm. of water; dynamics, normal; cell count, 30 red blood corpuscles per cu. mm.; Pandy test, 4 plus; total protein, 62 mg. per cent. Electroencephalographic studies showed evidence of a large deep-seated infiltrating tumor in the left frontal region spreading toward the deeper portion of the left temporal region. X-ray examination of the skull revealed decalcification of the dorsum sellae and the posterior clinoid processes with suggestive decalcification of the floor of the sella turcica.

*Course:* On the third day in the hospital the patient was subjected to a left fronto-temporal craniotomy. At operation the inferior frontal convolution felt harder than normal. A transcortical incision was made, and in its posterior portion several pieces of tumor tissue were removed from a depth of 3 to 4 cm. It was felt that the tumor was a spongioblastoma and therefore radical surgery was not attempted. The day after operation the patient had a right hemiplegia, was completely mute, and respirations were Cheyne-Stokes in character. A lumbar puncture revealed bloody cerebrospinal fluid under an initial pressure of 340 mm. of water; on removal of 20 cc. of cerebrospinal fluid the pressure dropped to 60 mm. of water. During the next few days the patient became somewhat more

alert but remained drowsy and mute. Successive lumbar punctures revealed xanthochromic cerebrospinal fluid under increased pressure. On the tenth day after operation the temperature rose to 103°F. and examination of the lungs showed evidence of consolidation. Following the administration of sulfathiazole the temperature returned to normal.



FIG. 1. Case 1. Spongioblastoma ependymale. Coronal sections of the brain showing the appearance and location of the tumor.

On the nineteenth postoperative day, the patient became stuporous, and developed a feeble pulse; her respirations then became increasingly irregular and she expired.

*Necropsy Findings: Brain.* *Gross:* There was considerable swelling of the gyri of the left hemisphere and the corresponding sulci were obliterated. The left side of the brain

was dark red and there was a small subarachnoid blood clot overlying the middle frontal gyrus.

When the brain was sectioned a large tumor mass was found involving primarily the left thalamus (fig. 1 upper), but also extending laterally to involve the left internal capsule, corpus striatum and part of the left parietal lobe. The tumor seemed to follow the course of the sulcus terminalis. It extended posteriorly as far as the beginning of the posterior horn of the lateral ventricle (fig. 1 lower). Anteriorly it extended to about the level of the precentral gyrus. The tumor had a yellow, granular, friable surface. There was bilateral internal hydrocephalus with slight asymmetry, the left ventricle having been compressed by the tumor. There was also some displacement of the ventricular system to the right.

*Microscopic:* The tumor is densely cellular. Running throughout the tissue there are many small blood vessels, and in some areas the tumor cells are arranged in pseudo-rosette

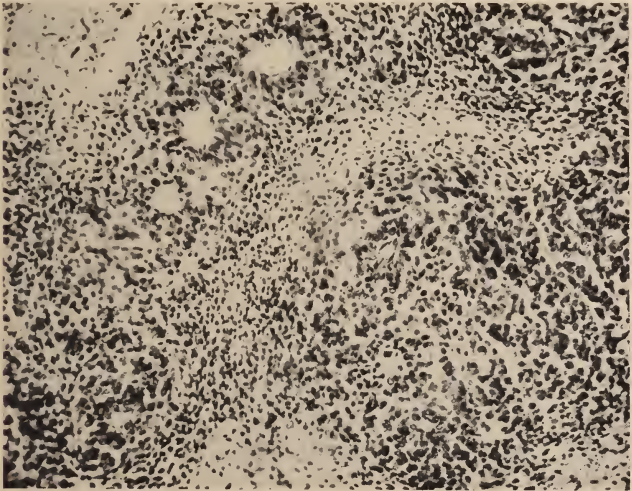


FIG. 2. Case 1. Spongioblastoma ependymale. Section of the tumor, showing its cellular type and arrangement. Hematoxylin and eosin stain, photomicrograph,  $\times 150$ .

forms around blood vessels (fig. 2). Some of the tumor cells are columnar, others spindle-shaped with fairly thick processes at each end. The nuclei are round or oval and have a dense chromatin reticulum. Numerous mitotic figures are seen. Some of the sections show numerous choroid villi (fig. 3) and in some areas of these sections there is a gradual transition between the tumor cells and the ependymal cells lining the choroid villi (figs. 4 and 5). Within the tumor there are also some large areas of necrosis. Sections of the pituitary gland show replacement of the posterior lobe and pars intermedia by tumor tissue. In one area there is a moderate invasion by the tumor cells of the anterior lobe of the pituitary gland. Nissl preparations of the tumor tissue show no neuroblastic elements.

*Comment.* Dr. Globus: The main object in presenting the foregoing case as well as subsequent cases of brain tumor in this series is to demonstrate the inter-

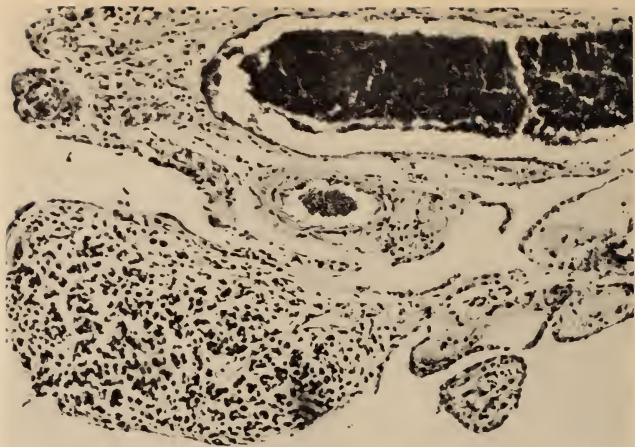


FIG. 3. Case 1. Spongioblastoma ependymale. Section exhibiting a small tumor nodule in the neighborhood of the choroid villi, showing the direct relationship between the ependymal lining of the latter and the tumor nodule. Hematoxylin and eosin stain, photomicrograph,  $\times 117$ .

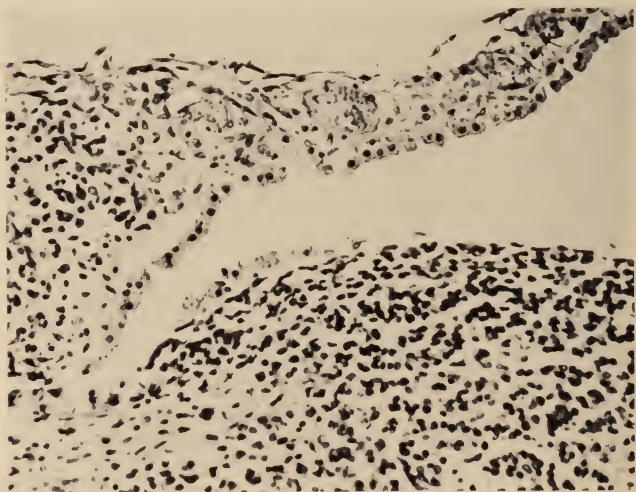


FIG. 4. Case 1. Spongioblastoma ependymale. Section under higher magnification showing the relationship of the ependymal lining to, and its direct continuity with, the cells of the tumor nodule shown in figure 3. Hematoxylin and eosin stain, photomicrograph,  $\times 200$ .

relationship of primary neuroectodermal tumors of the brain and trace them through their somewhat divergent lineage to the early primordial cell forms. It has already been shown by me (1) as well as by others that the so-called gliogenous tumors, no matter what their ultimate type, are traceable to primitive neuroectodermal cell forms of either spongioblastic or neuroblastic lineage. It has also been shown that the embryonal rest theory offers the best explanation for the several forms of brain tumor of neuroectodermal variety and for the divergence in their cellular make-up. Thus, we have come to recognize primary tumors of the brain which consist predominantly of undifferentiated glial elements or the so-called spongioblast, spongioblastoma to which often the modify-

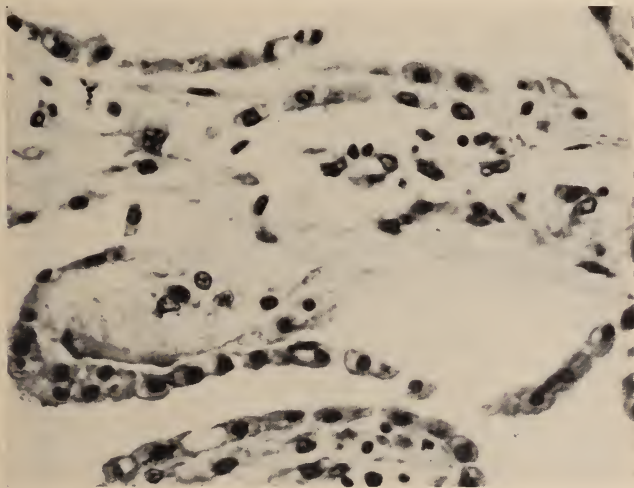


FIG. 5. Case 1. Spongioblastoma ependymale. An area of the section shown in figure 4, displaying the low cuboidal (ependymal) cells under higher magnification. Hematoxylin and eosin stain, photomicrograph,  $\times 525$ .

ing adjective ependymale is added to indicate the preponderance of ependymal spongioblasts within such a tumor. Such a tumor is typified by Case 1. Another form of spongioblastoma, which is often spoken of as spongioblastoma multiforme (illustrated in Case 2), is the type of neoplasm in which there is great variability in the stage of differentiation or maturity of the spongioblastic elements, but above all there is a large quota of giant cells. It is assumed that the latter, by their mitotic or amitotic division, are mainly responsible for the rapidity with which the cells multiply and the tumor grows. Then there is another type of tumor for which the term spongioneuroblastoma has been adopted by me. This, as the name indicates, consists of many varying quotas of spongioblasts

and neuroblasts with an admixture of more mature forms. This is also a more or less rapidly growing tumor. We then come to two others tumor forms—transitional glioma and transitional glioneuroma as typified by Cases 4 and 5. In both tumor types the glial and the neuronal elements have acquired a somewhat higher stage of differentiation, approximating a mature form of glial and nerve cell. However, both tumor forms still contain a fairly large contingent of unripe spongioblasts and neuroblasts in various stages of transition toward the more mature cell forms.

Returning to Case 1, particular attention should be drawn to figures 3, 4, and 5 in which the transition of fairly normal ependyma can be traced to the cells of the main tumor mass as well as to those of smaller tumor nodules.

Reported by *S. Levin, M.D.*

### *Case 2. Spongioblastoma Multiforme*

*[From the Neurosurgical Service of Dr. Ira Cohen]*

*History:* (Adm. 474856; P.M. 11899). A man, aged 47 years, was apparently well until one year prior to admission to this Hospital (June 14, 1941). He then began to display a dulling of intellect and a disinterest in his surroundings. Seven weeks before entering the hospital he experienced an episode of transient blurring of vision in the right eye lasting about five minutes. Three weeks later he began to complain of severe right sided headaches. His vision became blurred in both eyes and a rapid and progressive impairment of memory was noted. There also appeared a hesitancy of speech which at first occurred in brief episodes, but then progressed so that it soon seriously impaired his ability to express himself. He vomited frequently and experienced marked anorexia during the latter part of his illness. In the course of eight weeks before admission he lost ten pounds.

*Examination:* The patient was well developed but poorly nourished. He did not appear acutely ill. There was slight tenderness to percussion over the right parietal region. He was mentally dull and aphasic (the patient was right handed). He groped for words, and had anomia, acalculia, and echopraxia. There was bilateral papilledema and slight left central facial paresis. The deep reflexes of the left arm were more active than the right, but those of the right leg were more active than the left. A suggestive right Babinski sign was found. The abdominal reflexes were depressed bilaterally, more so on the right side. Slight weakness was present on the right side of the body. There was questionable astereognosis and diminution of position sense in the left hand with hypalgesia over the entire left side of the body. The blood pressure was 140 systolic and 82 diastolic. The pulse rate was consistently between 60 and 70 per minute.

*Laboratory Data:* Urine, negative. Blood: Cytology, chemistry, and serology, negative. Cerebrospinal fluid: Pressure and dynamics, normal; total protein, 72 mg. per cent; Pandy reaction, 4 plus; cell count, 8 lymphocytes per cubic millimeter; serology, negative. Electroencephalogram was interpreted as suggesting a focus deep in the right temporal lobe, probably an infiltrating expanding lesion. X-ray examination of the skull showed only slight decalcification of the posterior clinoid processes. X-ray examination of the chest was normal.

*Course:* In view of the aphasia an expanding lesion in the left fronto-parieto-temporal region was considered. As this did not account for the left sided signs, a "crossed aphasia"

was postulated. Pneumoencephalogram showed the left lateral ventricle to be dilated and markedly displaced toward the left. The third ventricle was sickle-shaped and also displaced toward the left. The appearance was that of a large expanding lesion in the right cerebral hemisphere. One week after the patient entered the hospital a right temporo-parietal craniotomy was performed. The middle temporal convolution appeared flattened and widened. Aspiration with a brain canula did not disclose a cyst. A hard resistance was found at a depth of about 5 cm. A transcortical incision was made through the center of the middle temporal convolution and a hard yellowish-gray, well demarcated neoplasm, measuring about 4 x 3 x 2 cm. was found; the tumor was removed with curettes and suction. A small decompression was left in the temporal region. Following the operation the patient failed to respond and expired 36 hours later.

*Necropsy Findings: Brain.* Gross: There was a small amount of subdural clot underlying the bone flap. The brain was enlarged asymmetrically, the right hemisphere being

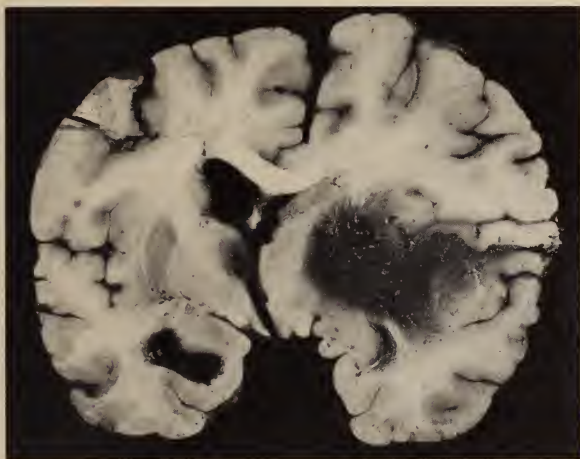


FIG. 6. Case 2. Spongioblastoma multiforme. Coronal section of the brain showing the gross appearance and location of the tumor.

larger than the left. There was an operative defect 6 cm. long in the right fronto-temporal region.

When the brain was sectioned, a large area of discoloration with a cerebral core of deep red friable tissue was seen in the right cerebral hemisphere. It was most prominent in the region of the corpus striatum opposite the island of Reil (fig. 6). A wide zone of edema surrounded it antero-posteriorly. The area of discoloration extended from about the level of the anterior commissure back to a point on a level with the posterior commissure. Another area of discoloration was found on the medial aspect of the left thalamus, near the massa intermedia. There was a blood clot in the lateral portion of the left hemisphere resulting from a ventricular puncture.

*Microscopic:* The tumor tissue has a highly cellular structure. Its central area is necrotic. The cells of the tumor are pleomorphic without any characteristic relation to the blood vessels or to one another. Many large multinucleated giant cells are seen, their

nuclei arranged in a cluster at one end or ring-like at the periphery of the cell (fig. 7). A few monstrous giant cells are present, their single nuclei being four to five times as large as the average nucleus. Some of these cells are pyriform and send off long processes but contain no Nissl substance. Mitoses in all stages are seen. The blood vessels of the tumor are moderately thick. The brain tissue adjacent to the tumor is edematous and disorganized. Many of the blood vessels at the periphery of the tumor are partly or completely thrombosed and cellular exudates in the perivascular spaces are frequent. Examination of the small discolored area in the left thalamus adjacent to the massa intermedia reveals a circumscribed area of encephalomalacia.

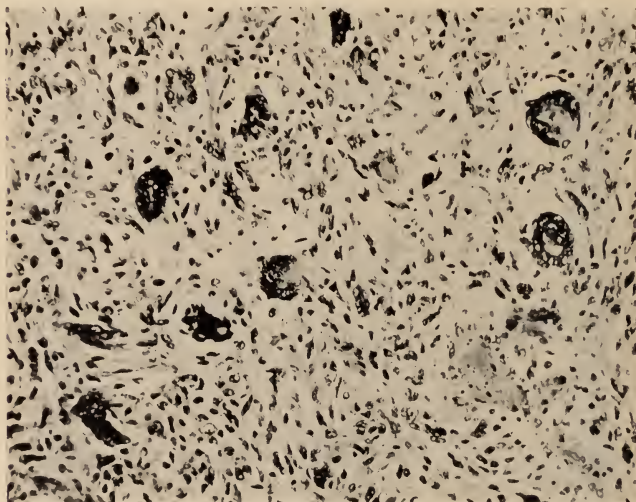


FIG. 7. Case 2. Spongioblastoma multiforme. Section of the tumor, showing the large quota of typical giant cells. Hematoxylin and eosin stain, photomicrograph,  $\times 150$ .

*Comment.* Dr. Globus: In this case particular attention is drawn to the large number of giant cells as shown in figure 7, which characterizes the gliogenous tumor designated as spongioblastoma multiforme (2).

Reported by A. Kazan, M.D.

### Case 3. Spongioneuroblastoma

[From the Neurosurgical Service of Dr. Ira Cohen]

*History:* (Adm. 474177; P.M. 11879). A man, aged 54 years, was said to have been in apparent good health until three weeks prior to admission to the hospital (May 31, 1941) when he began to complain of intermittent right sided headaches. At first these lasted only about five minutes, but soon they became more pro-

tracted and very severe. During that period it was noted that his face became asymmetrical and weakness of the left arm and leg developed. Within one week after the onset of the weakness he became confined to bed. He also became

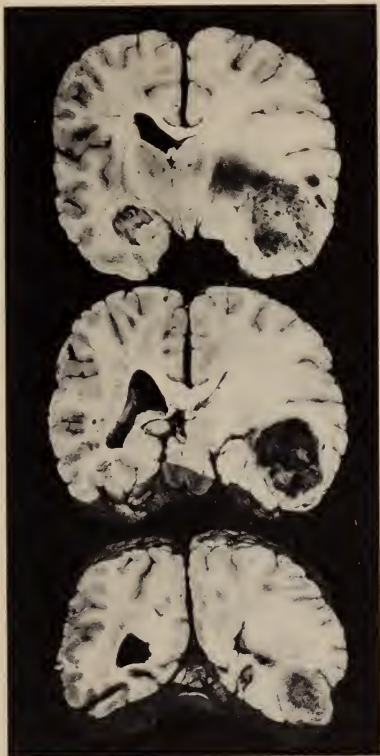


FIG. 8. Case 3. Spongioneuroblastoma. Coronal section of the brain showing the gross appearance and location of the tumor.

drowsy and uncooperative and complained of diplopia. On one occasion he vomited forcefully. (He was right handed.)

*Examination:* His mental state was one of torpor; when aroused he was found to be well oriented, revealing no marked memory defect. He chose monosyllabic words in replying to questions and followed simple directions very poorly. The nasal margins of both discs

were blurred. The pupils were equal, but small; they reacted poorly to light. The visual fields were grossly normal. There was left hemiparesis including the lower face with major involvement in the fingers of the left hand. All the deep reflexes were depressed. The abdominal and cremasteric reflexes were bilaterally absent; there was a left Babinski sign. Sensation was intact except for suggestive astereognosis in the left upper extremity.

*Laboratory Data:* Urine, 3 plus albumin. Blood: hemoglobin, 100 per cent; white blood count, 20,000; Wassermann reaction, negative. Cerebrospinal fluid: initial pressure, 220 mm. of water; final pressure, 70 mm. of water after the removal of 10 cc. of fluid; Ayala index, 3; Pandy reaction, 4 plus; 350 red blood cells in various stages of crenation; total protein, 157 mg. per cent; colloidal gold and Wassermann reactions, negative. Bedside x-ray examination of the chest revealed no abnormalities in the lungs.

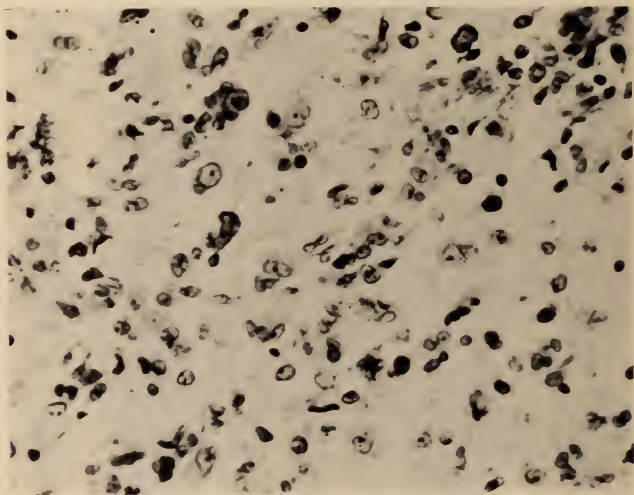


FIG. 9. Case 3. Spongioneuroblastoma. Section of tumor displaying its histologic character. Nissl stain, photomicrograph,  $\times 525$ .

*Course:* On the day following admission the patient lapsed into deep stupor and the left sided paresis became more marked. The pulse rate fell to 56 per minute. A right-sided sub-temporal decompression was then performed and the brain in the right temporal region was aspirated. No evidence of tumor was found. The patient remained comatose and died 12 hours later.

*Necropsy Findings. Brain. Gross:* When the brain was sectioned a tumor was found involving the posterior two-thirds of the right temporal lobe and occupying its entire width except for a narrow rim of cortex (fig. 8). The tumor measured 4 x 3 x 3 cm. The lateral aspect had a grayish pink mottled discoloration. The surface, particularly in the dorsal aspect, had areas of softening. The lateral ventricle on the ipsilateral side was compressed. The entire ventricular system was dilated and displaced to the left.

*Microscopic:* The tumor is made up of very pleomorphic cells, round or fusiform, massed around blood vessels in sheets and cords. The cells have fairly large clear nuclei, several containing a nucleolus (fig. 9) many mitotic figures are seen. A few cells containing pow-

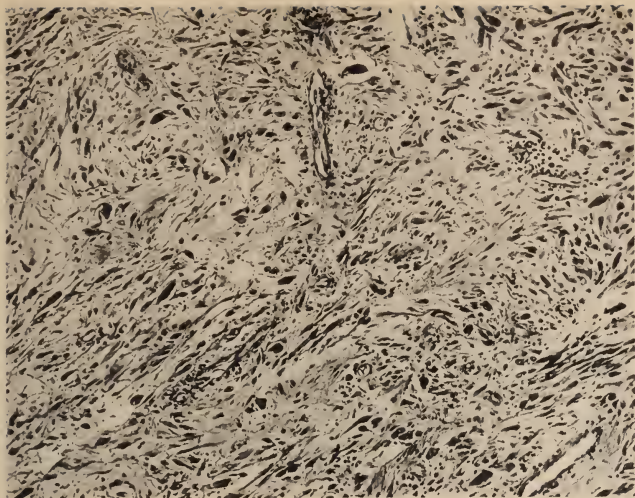


FIG. 10 A. Section of a spongioneuroblastoma showing the basket-like arrangement of the neuroblastic elements. Globus modification of the Hortega silver carbonate method, photomicrograph,  $\times 113$ .



FIG. 10 B. Section of the tumor under higher magnification of a selected small field in figure 10 A, showing the size and the character of the neuroblasts. A striking feature is the presence of a simple nucleolus in the fairly clear vesicular nucleus. Hematoxylin and eosin stain, photomicrograph,  $\times 850$ .

dery granular substance in the cytoplasm are noted in preparations stained by Nissl's method. There are also some very large cells which resemble swollen glia cells; these have homogeneous cytoplasm and contain fragmented nuclear material. The tumor cells are seen infiltrating the adjacent brain at the periphery of the lesion. The above described neoplastic zones are relatively few and are distributed like islands in the midst of extensive necrotic areas; the latter are composed either of amorphous hyaline material or of very cellular tumor tissue infiltrated by degenerating polymorphonuclear cells.

The blood vessels in the areas adjacent to the tumor present great thickening of their intima and adventitia; many of them have cuffs of red blood cells or lymphocytes. The vessels within the necrotic parts are thrombosed for the most part. In a few places blood channels are so increased as to resemble an angiomatous structure.

In addition to the above changes, the adjacent brain shows an increased gliosis; diminution of the number of neurones, and distortion of the remaining neurones.

*Comment. Dr. Globus:* This case is not the most typical form of spongioneuroblastoma for it lacks one of the most striking features of the tumor, the giant cells which are well shown in another tumor of the same variety (figs. 10 A and B). However, the presence of numerous unripe ganglion cells and an admixture of many undifferentiated glial cells justifies its grouping with the spongioneuroblastomas.

Reported by *P. Myerson, M.D.*

#### Case 4. Transitional Glioma

[From the Neurosurgical Service of Dr. Ira Cohen]

*History:* (Adm. 477428; P.M. 11939). A man, aged 40 years, was well except for occasional morning frontal headaches, until two weeks before entering the hospital (August 8, 1941), when he began to complain of inability to concentrate and inability to see distinctly. One week later he developed bilateral supereiliary headaches and became drowsy. He then began to have difficulty in naming objects and people, although he could apparently recognize them. The headaches became persistent, were relieved incompletely by medication, and were accompanied by a "kinking" sensation in the occipital region. There were no vomiting, weakness, tremors, convulsions, or paresthesias, and no personality changes were noted.

*Examination:* The ophthalmoscopic examination revealed swelling of both optic discs. Visual field examination showed a complete right homonymous hemianopsia with concentric sparing of the macula. A questionable right central facial paresis was noted. The knee and triceps reflexes seemed to be slightly increased on the right side, and there was a diminished plantar reflex with a questionable Babinski sign on the left. There was a marked aphasia consisting of alexia, acalculia, agraphia, and anomia, the most prominent of which was the anomia. There was also finger agnosia and difficulty in carrying out complex commands. Orientation was intact. The blood pressure was 120 systolic and 70 diastolic.

*Laboratory Data:* Urine, negative. Blood: cytology, chemistry and serology, negative. Cerebrospinal fluid: clear, and colorless; initial pressure, 100 mm. of water; dynamics, normal; total protein, 50 mg. per cent. X-ray examination of the skull showed the pineal gland to be shifted to the right about 1 cm. Electroencephalographic studies were interpreted as indicating an "infiltrating tumor in the left temporal lobe extending more toward the occipital than the parietal region."

*Course:* A diagnosis of tumor in the region of the left angular and supramarginal gyri was made. One week after the patient's admission to the hospital a left parietal craniotomy was performed. The dura was tense; when it was opened the underlying gyri appeared pale, wide and apparently under great pressure. A needle was inserted in the posterior part of the temporal lobe and a small cyst was found from which about 5 cc. of thick yellow fluid was aspirated. The bone flap was not replaced. In spite of the decompression, the patient failed to respond after the operation. He grew more drowsy, his temperature rose to 102.6° F., and he died the following day.

*Necropsy Findings. Brain. Gross:* The gyri in the left cerebral hemisphere were increased in size and flattened; the corresponding sulci were obliterated, particularly around the left angular gyrus, which was somewhat softened. On sectioning, the left cerebral hemisphere appeared to be larger than the right. Near the roof of the left lateral ventricle, at the junction of the parietal and occipital lobes, there was a tumor mass about

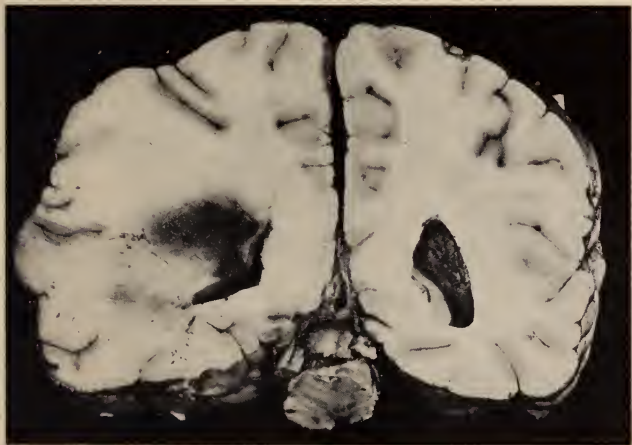


FIG. 11. Case 4. Transitional glioma. Coronal section of the brain, showing the gross appearance and location of the tumor as shown by the area of discoloration.

2½ cm. in length, reddish-brown in color and surrounded by an area of swelling and yellowish discoloration (fig. 11).

*Microscopic:* The tumor is densely cellular in most areas and has no definite structural pattern. The tumor cells and their nuclei show moderate variation in size and shape. Some of the nuclei have a fairly dense chromatin reticulum. Occasional multinucleated giant cells are seen. Mitotic figures are fairly numerous (fig. 12). The tumor contains a moderate number of small blood vessels, several of which show fairly marked endothelial proliferation. Silver stains reveal a moderate number of glial elements.

*Comment. Dr. Globus:* The striking feature of transitional glioma is the type of vessel which is usually encountered as seen in figure 12. The vessels are rather numerous, establishing a well organized wall, displaying proliferative tendencies of the vascular endothelium. The same figure discloses numerous

mitotic figures indicating that the transitional gliomas are also of a malignant character, in spite of the many fairly mature glial elements found in such tumors

Reported by *E. Rinzler, M.D.*

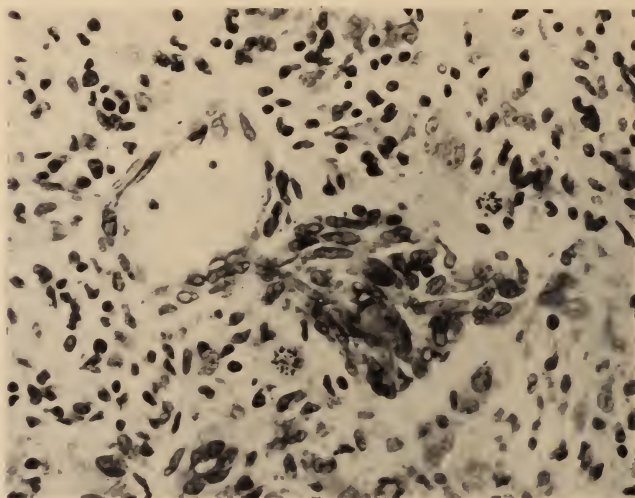


FIG. 12. Case 4. Transitional glioma. Section of the tumor, displaying the proliferative character of vascular endothelium and the many mitotic figures. Hematoxylin and eosin stain, photomicrograph,  $\times 505$ .

#### Case 5. Transitional Glioneuroma

[From the Neurosurgical Service of Dr. Ira Cohen]

*History:* (Adm. 482191; P.M. 12036). A man, aged 51 years, was apparently well until five weeks before admission, when he became listless, wandered about aimlessly and lost interest in his environment. Four weeks later he refused to shave himself because of weakness of his hands and numbness of the right side of his face. It was then noted that his smile was "crooked", his mouth being drawn to the left. Two days before admission he became drowsy, confused, could not express himself or answer questions and was incontinent at times.

*Examination:* The patient was apathetic, disoriented for place and person, and showed impairment of recent and remote memory. There was acalculia and anomia and some sensory paraphasia. The optic discs were negative and there was a suggestion of a right homonymous hemianopsia. A right central facial weakness was present, as well as weakness and spasticity of the right arm and leg. The deep reflexes on the right side were greater than on the left; the abdominal and cremasteric reflexes were absent.

*Laboratory Data:* Urine, blood cytology and serology were negative. Cerebrospinal

fluid: Initial pressure, 160 mm. of water; final pressure, 80 mm. of water after removal of 10 cc. of fluid; dynamics, normal; Ayala index, 5; total protein, 67 mg. per cent. The

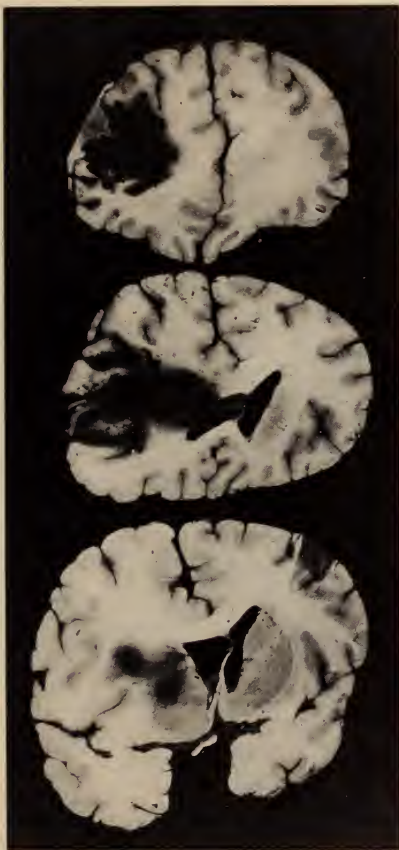


FIG. 13. Case 5. Transitional glioblastoma. Coronal sections of the brain showing the extent and gross appearance of the tumor.

electroencephalographic record was interpreted as suggesting an infiltrating growth in the left frontal lobe near the midline. X-ray examination of the skull showed an irregular area of decreased density in the left parietal region. A pneumoencephalogram showed

both lateral ventricles displaced to the right with compression of the anterior horn of the left lateral ventricle and displacement of the third ventricle to the right. There was no air over the left cortex.

*Course:* A rapidly growing neoplasm, gliogenous or metastatic in character was considered. A left fronto-temporal craniotomy was done and an infiltrating tumor in that area was removed partially. Within the tumor a cyst was found containing about 20 cc. of reddish brown fluid. Following the operation, the patient lapsed into coma, and the next day his temperature rose to 104°F. There was spasticity of the extremities, on the right more than the left and the left pupil was larger than the right. The patient expired on the third postoperative day.

*Necropsy Findings. Brain. Gross:* When the brain was sectioned a large crater-like defect was found on the left frontal lobe. It extended for a distance of several centimeters

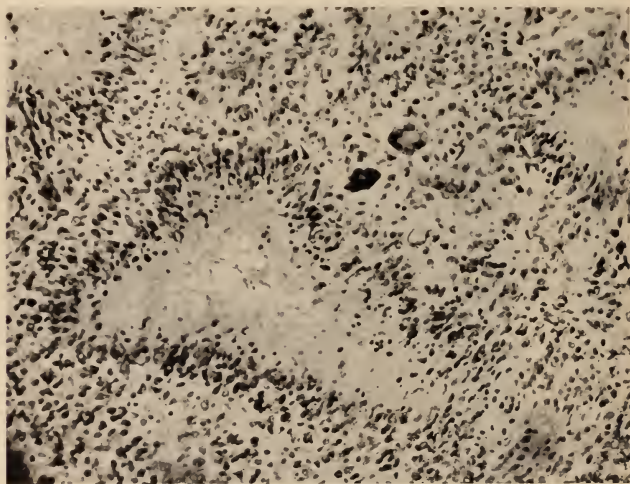


FIG. 14. Case 5. Transitional glioblastoma. Section of the tumor, exhibiting the palisade arrangement of the tumor cells about necrotic zones, a feature noted in all of the more malignant neuroectodermal brain tumors. Nissl stain, photomicrograph,  $\times 150$ .

beginning at a point about 1 cm. in back of the frontal pole and extending as far back as a point on the level with the formation of the head of the caudate nucleus. The crater-like defect measured about 3 cm. in its widest portion in the vertical plane and about 2½ cm. in the horizontal plane. It was fairly well demarcated from the adjacent intact brain tissue. At the level of the anterior end of the internal capsule there was a little grayish rounded area which produced slight elevation at the sulcus terminalis. The tumor at this point involved the corpus callosum and projected into the anterior horn of the left lateral ventricle (fig. 13).

The ventricular system was shifted to the right. The homolateral anterior horn was wider than the contralateral one. The former was widest on its roof, while the latter seemed to be elevated and was compressed. Further anteriorly the anterior horn of the homolateral ventricle was somewhat depressed as well as shifted to the right.

A small area of softening was found in the basis mesencephali on the right side.

*Microscopic:* Sections of tumor tissue, cerebral cortex and pituitary gland are stained with hematoxylin and eosin. Sections of the tumor tissue show it to be densely cellular and infiltrating the surrounding cerebral cortex. There is fairly marked variation in the size and shape of the tumor cells and their nuclei. Several multinucleated giant cells are present. A moderate number of mitotic figures are seen. The tissue also shows numerous blood vessels of moderate caliber with endothelial proliferation. Within the tumor there are several small areas of necrosis with dense palisades of nuclei surrounding them (fig. 14); some of these necrotic areas contain free blood. The pia-arachnoid over the neighboring cortex shows considerable thickening and increased cellularity. Some blood red cells and macrophages containing brown pigment are scattered through its meshes.

Silver stains show many glial elements with a predominance of unipolar and bipolar spongioblasts. Cajal stain shows a moderate number of atypical astrocytes with thick processes. Nissl preparation shows a few small neuroblastic elements.

*Comment. Dr. Globus:* In the transitional form of glioneuroma one sees practically all that is encountered in the spongioblastoma multiforme as well as the spongioneuroblastoma except that the cells have assumed a more advanced stage of differentiation, but even in these tumors one still encounters some of the features which are characteristic of the spongioblastoma multiforme such as palisading of nuclei around necrotic areas as shown in figure 14.

Reported by *J. E. Rubinstein, M.D.*

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## CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, October 23, 1940*

### Common Duct Stone Giving Rise to Cholangitis and Acute Ascending Suppurative Pancreatitis

*[From the Surgical Service of Dr. Ralph Colp]*

*History* (Adm. 462639; P.M. 11615) A 58 year old laborer was in good health until one year before admission, when he had an acute illness characterized by vomiting, diarrhea and abdominal pain. He was admitted to another hospital, where a diagnosis of "ptomaine poisoning" was made. Thereafter he suffered repeated mild attacks of eructation and epigastric oppression following ingestion of fried or fatty foods. Three days before admission to this hospital, he was awakened from sleep by very severe pain in the epigastrium, radiating to the back and along the costal margins. This lasted for one hour, subsided, only to recur. He was nauseated, but did not vomit. The urine became dark in color; the skin yellow. No stool was passed. He had fever, but no severe chill.

*Examination.* The patient was an acutely ill man, dyspneic on slight exertion, but not while at rest. The temperature was 103.4°F. The skin and sclerae were moderately icteric. The tongue was heavily coated. Over both lung bases, scattered moist rales were heard. The heart was not enlarged; rate 112 per minute, rhythm irregular. The blood pressure was 160 systolic and 100 diastolic. The abdomen was tense throughout, and rebound tenderness was elicited everywhere. There was rigidity and marked tenderness in the right upper quadrant and epigastrium. No masses could be palpated, and there was no evidence of fluid.

*Laboratory Data.* Urine: 1 plus albumin, 3 plus bile, 1:10 urobilin. Blood: Hemoglobin, 123 per cent; red blood cells, 6,360,000; white blood cells, 9,700 with 16 per cent non-segmented and 66 per cent segmented polymorphonuclear leucocytes. The prothrombin index was 100 per cent. The icterus index was 27; blood urea nitrogen 9 mg. per cent; sugar 150 mg. per cent; blood cholesterol 190 mg. per cent, esters 65. Blood culture was sterile. The blood Wassermann reaction was negative. The stool gave a strongly positive reaction for urobilin. X-ray examination of abdomen disclosed no radiopaque calculus. Electrocardiogram showed auricular fibrillation, deep Q<sub>3</sub> and low T waves in all leads.

*Course.* The morning after admission, the patient had a shaking chill, followed by a temperature rise to 105°F. In view of the septic course, it was thought advisable to proceed with surgical intervention, despite the fact that the patient did not represent a good operative risk. Operation was performed on the third day of hospitalization. The gall bladder was found to be covered by omental adhesions, edematous and thickened. Three calculi were removed from the dilated common duct, and cholecystectomy performed. His condition seemed good during the first three postoperative days, although the temperature remained elevated between 102° and 103°F. Cultures of the blood remained sterile. The jaundice diminished and the icterus index fell to 10. No evident cause for fever, which was ascribed to a persistent cholangitis, was apparent. There was no abdominal tenderness, the common duct tube drained well. On the fourth postoperative day the patient suddenly became disoriented and violent. The temperature rose to 106°F. He was restrained with great difficulty; it became necessary to administer in-

travenous paraldehyde. An hour later, when the wound was inspected, omentum was found protruding through the widely separated edges. The wound was irrigated, packed, and again closed. He was placed in an oxygen tent and given morphine. The following day he appeared to be in shock. A small blood transfusion did not improve his condition appreciably. Approximately twenty-nine hours after the acute psychotic episode he again became violently agitated, and died suddenly on the ninth day after admission.

*Necropsy Findings.* Dr. Klempner. A small stone was lodged in the papilla of Vater. The common bile duct was dilated and inflamed. Over the *pancreas* many yellow areas of suppuration were seen. The pancreas was swollen and edematous, the cut surface revealed many small abscesses. There was relatively little pancreatic fat necrosis. An incidental finding was a diverticulum of the *duodenum* just below the papilla of Vater. The *heart* showed an area of fibrosis in the right ventricle due to occlusion of the right coronary artery. Myocardial fibrosis limited to the right ventricle is unusual. A large ante-mortem clot was present in the main pulmonary artery and its right branch. The essential findings are those of acute suppurative pancreatitis due to ascending infection.

*Comment.* Dr. Bachr. A question of interest is: did the patient expel the calculi from the gall bladder into the common bile duct three days before his admission to the hospital, causing the ascending infection, or did the expulsion and common duct obstruction occur at the time of the acute illness one year ago? I believe that the dilatation of the common duct indicates that the biliary obstruction was of rather long duration, and that the recent acute illness was due to the ascending cholangitis and intense pancreatic infection. It is not uncommon for calculi to enter the common duct and remain symptomless for months or years.

Reported by Edward B. Grossman, M.D.

Wednesday, November 13, 1940

Amyloidosis Secondary to Malignant Grawitz Tumor (Hypernephroma)  
of the Kidney. Death from Uremia Due to Amyloid Disease of  
the Kidney

[From the Medical Service of Dr. B. S. Oppenheimer]

*History* (Adm. 459740; P.M. 11566). A woman, aged 84 years, had been in this Hospital thirty years before for the removal of a fibroid uterus. She was apparently well thereafter except for rheumatism until the onset of her present illness. About three months before admission she began to complain of anorexia and constipation. The anorexia was progressive and, in the three weeks preceding admission, was associated with nausea and vomiting. Her diet up to the onset of symptoms was fairly well varied except for abstinence from vegetables. With the onset of anorexia and nausea, her food intake decreased sharply. For the three weeks preceding admission there was burning of the tongue and dryness of the lips. The constipation had also become more marked and there was no bowel movement for three days. In the course of two years there had been a weight loss of fifty pounds. A gastro-intestinal series at another institution was said to be negative. The patient was admitted to this hospital on July 12, 1940.

*Examination.* The patient was a dark-skinned, elderly woman with evidence of recent weight loss. There was marked arcus senilis. The pupils were normal; the conjunctivae were pale. The fundi showed narrowed arteries. The mouth was edentulous. There was atrophy of the papillae of the tongue; on the tongue was a central, broad, red, smooth area. The lips showed fissuring at the angles. The lungs were normal. The heart sounds were of good quality; rhythm was regular. The blood pressure 130 systolic and 60 diastolic. The abdomen showed a well-healed midline suprapubic scar. The liver was palpable three finger-breadths below the costal margin. There were well advanced osteoarthritic changes in the joints. The deep reflexes of the arms and the ankles were not obtained; the knee jerks were feeble. The impression was that of avitaminosis B; hypertrophic arthritis; and suspicion of abdominal malignancy.

*Laboratory data.* Blood: hemoglobin, 74 per cent; red blood cells, 3,250,000; white blood cells, 16,500 with 74 per cent polymorphonuclear leucocytes, 11 per cent lymphocytes, 5 per cent monocytes, and 3 per cent eosinophiles. Urine specific gravity varied on casual specimens from 1.003 to 1.016; the albuminuria varied from negative to 3 plus; microscopically there were some granular casts, many white blood cells and occasional red blood cells. Esbach determinations showed 4 grams per liter. Phenolsulphonphthalein tests showed less than 1 per cent excretion. Cystoscopy showed normal bladder and ureteral orifices and no obstruction to the passage of the ureteral catheters. No indigo carmine was seen in the urine after fifteen minutes. Urine was negative for Bence-Jones protein. Stool guaiac reaction was negative. Blood chemistry showed an elevated urea nitrogen of 67 mg. per cent; creatinine 4 mg.; blood sugar 120 mg.; calcium 11.8 mg. per cent. Blood Wassermann reaction was negative. X-ray studies showed normal heart and lungs, and a negative barium enema. The intravenous pyelogram did not visualize either upper urinary tract. Both kidney outlines appeared normal in position, size, and shape. There was no definite evidence of a urinary calculus. The electrocardiogram showed a QRS of moderately low voltage with inverted  $P_3$  and  $T_3$ .

*Course.* The blood chemistry findings clearly pointed to the presence of renal azotemia and acidosis. The patient was accordingly treated with intravenous fluids. At first the blood urea nitrogen fell to as low as 37 mg. per cent, but then rose steadily reaching 80 mg. per cent; the creatinine rose from 4 to 10.7 mg. per cent, whereas the carbon-dioxide combining power fell to 13.8 volumes per cent. In conjunction with this the patient developed marked oliguria, became edematous, distended, and developed Kussmaul breathing. The general condition steadily deteriorated and the patient died in pulmonary edema, three weeks after admission.

The cheilosis and tongue lesions which were present on admission responded well to rather large doses of vitamin B complex and cleared within a few days.

Because of the maintenance of a normal blood pressure which never rose higher than 140 systolic and 70 diastolic in the face of a progressive uremia, it was suspected that the renal lesion was either extrinsic (such as blocked ureters) or that there was intrinsic interference with the elimination of urine such as polycystic kidney or amyloidosis. The extrinsic factor was eliminated by the normal cystoscopy; the kidneys could not be palpated, thus militating against the diagnosis of polycystic kidneys. The patient soon became too ill to do a Congo red test, nor was there any clinical evidence to suggest an etiologic basis for amyloidosis.

*Necropsy findings.* *Dr. Klemperer.* The right kidney was enlarged, weighing 360 grams. Its upper pole was occupied by a large tumor which was not too sharply demarcated from the surrounding renal parenchyma. The neoplasm invaded and compressed the upper calyx. The tumor itself was yellow on section with many hemorrhagic areas interspersed. Microscopic examination confirmed the fact that it was a Grawitz tumor. The rest of the kidney had a waxy, yellow-gray color. The cortex was not narrowed, in fact in some areas it appeared wider. The left kidney had a similar appearance. It had the classical waxy color seen in amyloidosis. The amyloidosis involved not only the kidneys but all organs, chiefly the *spleen, adrenals, liver, and blood vessels.* The heart showed evidence of an acute

fibrinous pericarditis, indicative of the presence of a terminal uremia. There were no metastases.

Amyloidosis is associated with malignant tumors. This is not uncommon as exemplified here, with Grawitz tumors which undergo so much degenerative change.

*Comment. Dr. Baehr.* This patient died indirectly as a result of the tumor. The neoplasm underwent prolonged and extensive degeneration; the products of this disintegration were absorbed, resulting in amyloidosis; the amyloidoid changes in the kidney led to renal insufficiency which in turn was the immediate cause of death.

Reported by *Max Ellenberg, M.D.*

## THE STORY OF THE MOUNT SINAI HOSPITAL

*The Story of The Mount Sinai Hospital, of which the first seven installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninetieth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.\**

*The Jews' Hospital in New York was incorporated in 1852 by a group of public-spirited citizens, and in 1855 the doors of its first building on West Twenty-eighth Street were opened to receive patients. Staffed by some of the most prominent physicians of the day, the institution soon proved itself an excellent testing ground for the new methods and techniques which were being introduced into the rapidly broadening practice of medicine and surgery. During the Boyne Day riots, the cholera epidemic, and the Civil War, the Hospital showed its readiness to serve in time of crisis. In 1866 it was given its present name, The Mount Sinai Hospital. By this time it was out-growing its first home, and in 1872 moved to larger quarters at Lexington Avenue and Sixty-sixth Street, where the expansion in organization paralleled its growth in size and in medical resources. Here during the next few years the Out-Patient Department was formally established as an independent entity, the Medical Board was organized, the House Staff was enlarged, and the Medical and Surgical Services were separated for the first time.*

### GROWTH AND DEVELOPMENT, 1870-1904

#### VIII

Separation of the Medical and Surgical Services was first instituted in 1877, and in the same year the organization of the House Staff was changed to accord with this division. An Admitting Physician, who lived outside the Hospital, was considered a member of the House Staff. He was to have "...morning and afternoon hours at his office and two hours daily at the Hospital for the examination of applicants, ... visit at their homes those patients unable to come in person, have supervision over diet and condition of wards." His salary was set at five hundred dollars a year.<sup>45</sup> There were to be four members of the House Staff, chosen as before by competitive examination. These were the Resident Senior and Junior Physicians, and Resident Senior and Junior Surgeons, all of whom lived in the Hospital. The terms later adopted were House Physician or Surgeon for the Senior, with the term "Resident" also dropped from the Junior's title.

Alfred Meyer, later a Consulting Physician to the Hospital, was the first

\* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete are welcome and may be addressed to the Historian of the Hospital.

<sup>45</sup> Minutes of the Board of Directors' Meetings, The Mount Sinai Hospital, February 4, 1877.

Junior Physician to serve under this plan. He has described the examination which was oral and given at the home of one of the examining doctors. One question dealt with the symptomatology, pathology, and complications of typhoid fever; another with the treatment of a pistol shot wound in the abdomen.<sup>13</sup> The applicant having the best mark had the choice of services, and until 1886 it was an unheard of event to choose surgery—eloquent testimony to the status of that branch of hospital service. In that year Howard Lilienthal, now Consulting Surgeon, made this unprecedented choice, which he subsequently said was received like “the equivalent of a social error.” But whatever the effect on the startled examiners, it was a decision he never had occasion to regret.<sup>10</sup>

At the end of a six month period the services interchanged, and at the end of the year each Junior—now advanced to Senior—returned to his original service. Thus two years comprised the term of internship. There were few rules for the House Staff. Their duties were many and varied. They ranged from admitting accident and emergency cases in the absence of the Admitting Physician to helping with the extraction of teeth in the Dispensary. Persuading families to allow post-mortem examination was another task which met with rather inconspicuous success.

Interns wore ordinary street clothes when on duty, as did the members of the Staff who appeared on rounds in the long frock coats of the period. One intern was dismissed because he insisted on wearing his slippers.<sup>13</sup> It was not until 1890 that a member of the House Staff introduced the now familiar white coat, at which one of his fellow interns was heard to mutter, “The next thing you know we’ll be marching into the wards with a fife and drum corps.”<sup>9</sup>

The House Staff plan as developed in 1877 provided for the granting of a diploma to graduates of Mount Sinai, and in 1885 one was presented to Josephine Walter, the first woman in the United States to serve a formal internship. Encouraged by Willard Parker, her family physician, and by Abraham Jacobi, Dr. Walter had studied at the New York Infirmary for Women. After she passed her House Staff examinations, the Mount Sinai Board of Directors considered the case of “Josephine Walter, an interne.” Since it was regarded as improper for a woman to serve on the Surgical Service, which the House Staff exchange of services necessitated, she was given a choice of being Assistant Admitting Physician or of serving in the children’s ward. She accepted the latter.<sup>46</sup>

Following the organization of the two separate services, there developed an increasing interest in new and specialized departments, a trend which was to continue during the Hospital’s stay on Lexington Avenue and which mirrored the growing tendency toward specialization throughout the field of medicine. The appointment of Emil Noeggerath as Gynecologist to Mount Sinai in 1877 marked a step in this direction, but by confining the Gynecological Department to its Dispensary Mount Sinai followed the general inclination of

<sup>46</sup> Dr. Josephine Walter, Reprint from the *Encyclopaedia of American Biography*, American Historical Society, 1937.

that period to regard diseases of women as so limited a specialty that dispensary care was considered ample. Selected cases admitted to the Hospital were sent either to the medical or the surgical wards. The prevailing fear of surgery naturally extended to gynecology and therefore operations were rare, especially in serious cases.<sup>47</sup>



Lean, tall, and melancholy,<sup>15</sup> "long fingered, clear-thinking," and a careful operator, Emil Noeggerath was considered one of the best diagnosticians in his field.<sup>15</sup> He was lured from a quiet country practice in a small town on the Rhine by the promise of a position in a university which was to have been organized in St. Louis. He arrived in New York with his family in 1857. Ill, with few resources, and ignorant of the language and customs of a strange country, he

<sup>47</sup> Mundé, Paul F.: Report of the Gynecological Service of Mount Sinai Hospital, from January 1, 1883 to December 31, 1894, New York, William Wood Co., 1895.

found that the plans for the university had failed to materialize. In due time, however, he managed to develop an excellent obstetrical and gynecological practice in New York.<sup>45</sup> With Abraham Jacobi he was co-author of the ill-fated work, *Contributions to Midwifery and Diseases of Women*, of which the authors were forced to sell eight hundred copies as scrap paper. Again with Dr. Jacobi, he helped to found the *American Journal of Obstetrics* in 1868.<sup>46</sup> Pioneer work in the study of gonorrhea, however, marks the apex of Dr. Noeggerath's scientific career. Seven years before Albert Neisser announced his discovery of the germ which causes gonorrhea, Emil Noeggerath, in 1872, published his work on *Latent Gonorrhea in Women*. He drew attention to the fact that even after active symptoms of gonorrhea disappear, the infection remains and is still contagious. He was in agreement with the view that the infection is caused by an organism which secretes itself in the mucous membranes. The majority of his colleagues were far from sharing his concept of the latency of the infection or of its relation to sterility. Long after Neisser's discovery Noeggerath's work was finally given its proper value.<sup>48</sup>

The first separate service for the care of children to be established in any New York hospital was organized at Mount Sinai in 1878. Its creation and maintenance were made possible by a legacy of twenty-five thousand dollars, left to the Hospital in that year by Michael Reese of California. The necessity for such a separate service had long been felt. The department in the Dispensary was not adequate to care for the number of children who came, among them many from the Hebrew Orphan Asylum a few blocks away. Nor was it satisfactory or desirable to send children into the general medical and surgical wards. Moreover, for eighteen years the Mount Sinai Staff had counted among its members the man who did more than any other to influence early pediatrics in America, and who had held the first chair in that field in the United States: Abraham Jacobi, Attending Physician since 1860.

Dr. Jacobi's massive leonine head, with its veritable mane of hair, topped a short slight body. His eyes were penetrating, his manner energetic. Gentle and kind, he nevertheless possessed a flashing wit that could cut as well as glitter. Although primarily a pediatrician and physician, Dr. Jacobi—like most practitioners of his day—also entered the field of surgery. It was not unusual for him to perform operations on the trachea in cases of diphtheria, and it is on record that he resected ribs for empyema and operated for cancer of the esophagus.<sup>49</sup>

A further step in the setting up of special departments was the organization of an eye service in 1879. Emil Gruening, appointed Attending Ophthalmologist, took care of ear, nose and throat cases as well. He was to be the first surgeon anywhere in the United States to perform an operation for mastoiditis.<sup>49</sup> William Holland Wilmer, a graduate of the Mount Sinai House

<sup>48</sup> Reichle, Herbert S.: Emil Noeggerath, Reprint Annals of Medical History, Vol. 10, No. 1.

<sup>49</sup> Libman, Emanuel: Notes from the Medical History of The Mount Sinai Hospital, 1912.

Staff, in 1887 became the first of Dr. Gruening's pupils and an assistant in his practice. Dr. Wilmer subsequently became a noted eye specialist in his own right, and in 1925 the Wilmer Institute at Johns Hopkins was established in his honor.<sup>50</sup>

Dr. Gruening was a short, compactly built individual with a fine scholarly profile<sup>51</sup> and the full beard of the period. His tremendous hands with their



*E. Gruening*

thick joints appeared massive in contrast to the smallness of his stature, and made his surgical skill all the more amazing. It was extraordinary to see the light, deft touch with which he performed operations on the eye, or on infants in cases of mastoiditis.<sup>51</sup> Dr. Gruening operating for cataract was "something

<sup>50</sup> Winn, Mary Day: Wilmer, Wizard of Sight, New York Herald-Tribune, October 13, 1929.

<sup>51</sup> Interview with Dr. Harold Neuhof, December 21, 1939.

never to be forgotten."<sup>10</sup> A description of his careful and conscientious performance is revealing, not only of the man, but also of surgery of those days:

"The Graefe knife was held in the mouth of the operator, its ivory handle projecting from the right, the keen blade from the left, barely missing the gray beard and luxuriant moustache. The local preparations of the operative field were made: the scrubbing and irrigation of the conjunctival sac, the insertion of the speculum. The corneal section was then skillfully executed and the knife at once conveniently replaced. The cystotome divided the capsule, usually after iridectomy, the lens was extracted and the bandage applied. Through it all gentle quiet conservation went on defying what would ordinarily be regarded as an impediment to speech. Although there had been apparent disregard of asepsis or antisepsis, not a single case of infection was observed by me. Gruening actually antedated Arbuthnot Lane in the details of aseptic procedure for no contaminated object ever entered the field of operation."<sup>10</sup>

The Mount Sinai Training School for Nurses, established when nursing education was still in its pioneer stage, was an experiment undertaken after considerable hesitation. In 1873 Bellevue Hospital had founded one of the first professional training schools in the country. The nineteen graduates of the first Bellevue class soon proved to the medical profession the tremendous advantage of having scientifically trained nurses take the place of the untrained, frequently careless and inefficient women who had previously cared for the sick. By 1880 there were in the United States fifteen training schools, and their graduates were in great demand, for every hospital struggled with problems resulting from an inadequate supply of capable, trustworthy nurses. The 1878 report of the Mount Sinai House Physician mentions "...the difficulty of obtaining good nurses," and in 1880 a similar report points out that: "On account of the introduction of trained nurses into some of the wards, the nursing has been conducted much better than formerly, and the Directors have reason to congratulate themselves upon the improvements made in this department." These nurses were undoubtedly graduates of the Bellevue School.

As early as 1878, five years after the founding of the school at Bellevue, a group of women who were members of the Mount Sinai Ladies' Auxiliary realized that it was desirable, and necessary, for the Hospital to train its own nurses. Under the guidance of Mrs. Alma de Leon Hendricks, a Director of the Auxiliary, plans were laid for such a school at Mount Sinai. Though shelved for a while these plans had an effect, for consciousness of the new trend in nursing had penetrated the Hospital. In 1880 the Medical Board sent a resolution to the Board of Directors "...regarding the establishment of a training school for nurses in connection with this Hospital."<sup>52</sup> As a result, a committee was formed of several Directors and members of the Ladies' Auxiliary to consider the advisability of the plan. A month later the committee reported to the Board that:

"It has been practically demonstrated in all the Hospitals of Europe and some in this country that regularly trained, skilled nurses not only materially relieve

<sup>52</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, Nov. 12, 1880.

pain and disease and are of vital assistance to the physician, but also greatly reduce the death rate therein by keeping the resident doctors fully posted on all that transpires during their absence and noting the progress of diseases and reporting same to them. It has been a matter of fact in Mount Sinai Hospital that great difficulty is encountered in obtaining thoroughly competent nurses to take charge of the wards. More particularly is this the case in the female department where the discharges have been the most frequent and the available supply not equal to the demand. Having this in mind your Committee feel that a necessity exists for regular, trained nurses, and such can only be obtained by the establishment of a school for that purpose, connected with the Hospital."<sup>53</sup>

Accordingly, in February of 1881, the Mount Sinai Training School for Nurses was incorporated "... chiefly at the instance of some ladies well known in the community for their interest in various charitable spheres."<sup>54</sup> An institution separate from, but cooperating with the Hospital, the School had its own Board of Directors all of whose members, until 1895, were women. Mrs. Florian Florance was the first President. Within a few years a closer relationship with the Hospital was established—a relationship which continues to exist today.

With eight probationers and four graduates from Bellevue Hospital the School organized a curriculum, modeled on the Bellevue plan, which would cover two years' training. The Superintendent was Kate Rich, a Bellevue graduate. The students received practical instruction in the female and children's wards of Mount Sinai, where the graduates acted as head nurses. Experience in obstetrical work was provided at the Ladies' Lying-in Society, the Nursery and Child's Hospital, and the New York Infant Asylum. Theoretical instruction was given by means of lectures supervised by a Committee on Instruction, which included two members of the School's Board of Directors and three members of the Hospital's Medical Board. The lectures included semi-weekly talks on "... outlines of anatomy; physiology of digestion, circulation and respiration; hygiene of infants and adults in health and disease."<sup>55</sup> A measure particularly progressive for those days provided that "each class also receive anatomical demonstrations on the cadaver."<sup>55</sup> At regular intervals lectures were given by members of the Staff: eleven on surgical emergencies; seven on medical emergencies; six on gynecology and obstetrics; six on bandaging and general surgical dressings; one on diseases of the eye and ear; two on diseases of the nose and throat.<sup>55</sup>

In the first two years of the School's existence forty-three pupils were accepted.<sup>55</sup> (In 1942 Mount Sinai's School of Nursing had a student body of 268.) A home for the nurses was set up in a private house at 850 Lexington Avenue, at Sixty-fourth Street. These accommodations soon proved inadequate, and a second high-storied, brownstone house was rented at 852 Lexington Avenue.<sup>13</sup>

The struggle of nurses to attain full professional responsibility was to extend

<sup>53</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, Dec. 12, 1880.

<sup>54</sup> Annual Report of the Directors of The Mount Sinai Hospital, Executive Committee Report, 1881.

<sup>55</sup> Biennial Report of Mount Sinai Training School for Nurses, 1881-1883.

over a span of many years. They were not prepared for the many responsibilities which now constitute a routine part of a nurse's training. In summing up the work of the School's first two years, Mrs. Florance was forced to admit that although "... those competent to judge have informed us that our nurses have both practical and theoretical facilities for instruction which are not surpassed," still the curriculum lacked "... opportunities for observing much acute surgery."<sup>55</sup> Nurses were not expected to be present at operations, and if they did find their way into the operating room it was simply by courtesy:

"Through the courtesy of the House Staff of The Mount Sinai Hospital, our nurses have been more frequently invited to attend operations and post-mortem examinations than formerly."<sup>56</sup>

Not until the nineties did graduate nurses participate in any of the functions of the operating team. Even then they did not hand instruments to the surgeon as they do today. That was the office of the Junior House Surgeon. The nurses were present to help with dressings,<sup>57</sup> and only in 1901 was the position of head operating room nurse instituted.<sup>58</sup>

Following the example of Bellevue, Mount Sinai in 1881 opened only the women's and children's wards to the pupils and graduates of the School. The following year the question arose whether or not the School was to provide a staff for the male wards which were still cared for by untrained orderlies. This was an extremely daring proposal. The Medical Board hedged and suggested that female nurses enter the male wards "under certain conditions."<sup>59</sup> The "conditions" were not defined. The Board of Directors was more blunt. It flatly refused such a proposal.<sup>60</sup> Three years later, in 1885, the School was given the care of the male medical wards. The male surgical wards, however, did not become a part of its responsibility until 1897, and then it would seem, only after the suggestion of "training junior doctors in nursing" was found impractical.<sup>61</sup>

*To be continued*

<sup>56</sup> Biennial Report of Mount Sinai Training School for Nurses, 1883-1885.

<sup>57</sup> Interview with Dr. Martin Ware, April, 1938.

<sup>58</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, Feb. 2, 1902.

<sup>59</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, June 27, 1881.

<sup>60</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, April 9, 1882.

<sup>61</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, Oct. 10, 1897.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Congenital Anomaly; Rotation of the Kidney.* G. D. OPPENHEIMER AND B. S. WOLF. J. Urol., 46: 17, July 1941.

A case report was presented describing an uncommon anomaly of rotation of the kidney (excessive dorsal rotation). The ureter descended from the mid-portion of the anatomic lateral border of the kidney which was also the site of calculous disease. The patient previously had a right subcapsular nephrectomy for advanced calculous pyonephrosis. Because of elevated calcium and phosphatase findings, parathyroid exploration had been performed without finding a tumor. Death followed operation on the unsuspected anomalous kidney. Post-mortem findings revealed that acute pyelonephritis and sepsis were the causes of death, and also explained the anomalous course of the ureter which had been discovered at operation.

The case represented an instance of congenital anomalous renal rotation in distinction to renal torsion. There are few reported examples of excessive dorsal rotation such as is here described. In this case the excessive dorsal rotation was about  $340^{\circ}$ , which permitted the ureter to emerge and descend from the lateral aspect of the kidney. The advantage of preoperative diagnosis of such an anomaly is of course apparent.

*Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids. Based on a Study of 65 Allergic Children Given a Third or "Repeat" Dose.* M. M. PESHKIN. Am. J. Dis. Child. 62: 309, August 1941.

From three to sixteen months after the completion of primary immunization with two 0.5 cc. doses of combined alum-precipitated diphtheria and tetanus toxoids 65 allergic children were given a third, or repeat, dose of 0.5 cc. The results of the antitoxin determinations show that the injection of a third dose of combined alum-precipitated toxoids into allergic children was followed in all instances by an adequate titer of tetanus antitoxin, which was higher and lasted for a much longer period than that which followed the second injection, even though the corresponding titer obtained within one month of the third injection, was the same or less.

The incidence of local reactions both after the third and after the first two injections was about 25 per cent. An elevation of temperature lasting about one day followed the administration of the third dose to 3 per cent of the children, as compared with an incidence of 1 per cent among those given two doses. No allergic reactions, such as urticaria or asthma, were encountered.

*Tattooing with Mercuric Sulfide for Treatment of Intractable Pruritus Vulvae and Ani: An Anatomico-clinical Study.* R. TURELL. Am. J. Obst. & Gynec. 42: 290, August 1941.

Histologic studies of skin tattooed with mercury sulfide for the treatment of intractable localized pruritus are presented. Massive deposition of the mercury sulfide in the upper portion of the corium with some deposit in the epithelium is seen immediately after adequate tattooing. Later, the mercury sulfide is localized in the corium in clumps of various sizes, having a slight but definite tendency to reach the deeper portion of the skin. Evidence of foreign body giant cell reaction commonly seen in the skin after introduction of other foreign substances intracutaneously has not been observed following tattooing with mercury

sulfide. It appears that the quantity and the distribution of the mercury sulfide deposited intracutaneously by tattoo can be correlated with its therapeutic effectiveness.

*Diseases of Colon and Rectum.* R. TURELL. Am. J. M. Sc. 202: 282, August 1941.

In this review the subject of proctologic disease is dealt with from a broad point of view. The discussion is confined to local anorectocolonic disease without systemic involvement; primary local disease with secondary involvement of distant regions, and local disease as an expression of systemic disease. The following subjects are discussed: (1) Neoplastic disease. (2) Diarrheas, a) bacillary dysentery; b) chronic ulcerative colitis; c) amebic colitis; and, d) mucous colitis. (3) Diverticulosis and Diverticulitis. (4) Tuberculosis. (5) Venereal diseases, a) venereal lymphogranuloma; b) gonorrhea; c) chaneroid, d) Vincent's infection; and, e) granuloma inguinale. (6) Neurologic investigation of the colon. (7) Megacolon. (8) Role of the colon in urogenital disease, a) urogenital complications of malignant disease of the rectum. (9) Anesthesia. (10) Pruritus ani. (11) Hemorrhoids. (12) Anal fissures, ulcers. (13) The pecten band. (14) Anal abscess and anal fistula. (15) Anal incontinence. (16) Injuries to the anus, rectum and sigmoid. (17) Pediatric proctology. (18) Miscellaneous considerations, a) clinical pathology; b) ambulatory operative treatment; c) sacrococcygeal (pilonidal) cysts and sinuses; d) rectal bleeding; e) effects of irradiation on rectum; f) colonic allergy; g) enterobiasis; h) intestinal and vaginal trichomonads; i) fecal impaction; j) mineral oil; k) gastro-intestinal manifestations of anorectal lesions; l) rectal absorption of sulfanilamide and its derivatives.

The bibliography includes 173 pertinent references.

*The Electroencephalogram of Normal Children.* N. Q. BRILL, AND H. SEIDEMANN. Am. J. Psychiat. 98:250, September 1941.

Normal children, when subjected to hyperventilation, showed in their electroencephalograms dysrhythmias which resembled those seen in adult epileptics. In general, the younger the child the greater was the tendency to develop the dysrhythmias, especially when slow activity was present in the spontaneous record. Forty per cent of the children between the ages of 4 and 6 years developed abnormal rhythms, while in only 9 per cent of the 10 to 12 year group did such changes appear. The curve of diminishing trend followed almost a straight line, except for a slight rise in the 12 to 13 year period. Normal adults rarely develop a dysrhythmia during hyperventilation. Because of the high incidence in children, the dysrhythmia cannot be considered abnormal. It seems to represent a tendency to the convulsive state which is gradually outgrown. This is in accord with the clinical observation that the convulsive threshold diminishes with advancing age. (Tetany has been excluded as the cause of the dysrhythmia produced by hyperventilation.)

Study of the alpha rhythm revealed that above the age of 9½ years, alpha frequencies below 8 per second were unusual, while below this age they did occur. In addition, there was an abrupt decrease in the incidence of waves of 2 to 6 per second frequency above this age. There was a tendency for the alpha activity to become more rapid and thus approach the adult level with advancing years. Associated with this there was a definite trend toward better regulation of the alpha activity.

*Dietary Treatment of Chronic Arthritis.* E. NEUWIRTH. Med. Rec. 154: 222, September 1941.

The arthritic patient must not lose ground through a restricted diet. To induce a high degree of bodily vigor and resistance, proteins, vitamins and minerals should be supplied in excess of the amounts necessary to meet the normal needs of the body. The vitamins are advantageously supplied in the form of the natural food sources which contain them in a ratio determined by nature itself.

*Indoluria in Rheumatoid Arthritis.* E. NEUWIRTH. J. Lab. & Clin. Med. 26: 1939, September 1941.

Free indole was shown to be present in the freshly voided urine samples obtained from 88 patients with rheumatoid arthritis.

*Bacteriology of Peptic Ulcers and Gastric Malignancies: Possible Bearing on Complications Following Gastric Surgery.* G. P. SELEY AND R. COLP. *Surgery* 10: 369, September 1941.

In order to investigate the possible relationship of the bacteriology of the stomach and duodenum to postoperative infections, aerobic and anaerobic cultures were made from all specimens removed by subtotal gastrectomy. Presumably pathogenic microorganisms were recovered in 88 per cent of the malignancies and 30 per cent of the benign ulcers.

There was a greater incidence of wound and intraabdominal infections in those cases in which positive cultures were obtained at operation. The presence of *B. welchii*, *B. coli* and streptococci (of all varieties) were particularly significant. Every patient in whom *B. welchii* was recovered at operation either developed some serious complication or died.

Several precautions and therapeutic innovations were suggested by this study: 1) Avoid contamination of the peritoneal cavity by gastric and duodenal contents; 2) Drain the peritoneal cavity when contamination occurs or when reliability suture line may be questioned; 3) Use of *B. welchii* antitoxic sera is under consideration and 4) Preoperative use of sulfanilamide to be tried in gastric cases.

*Sternal Marrow Changes During First Week of Life. Correlation with Peripheral Blood Findings.* L. M. SHAPIRO AND F. A. BASSEN. *Am. J. M. Sc.* 202: 341 September, 1941.

Of greatest importance in this study which correlates sternal puncture with peripheral blood findings in 35 normal newborns, is the fact that at one week of age there is a marked drop in the marrow erythroid elements, reflected peripherally by the known drop in reticulocytes. The idea is offered that the fall in red blood cells and hemoglobin which takes place after birth is primarily the result of physiologic disintegration of the superabundant red blood cells carried over from fetal life, in the presence of diminished erythropoiesis.

*Amenorrhea due to Tuberculous Endometritis.* R. I. WALTER, U. J. SALMON, AND S. H. GEIST. *Am. J. Obst. & Gynec.* 42: 505, September 1941.

The authors present the report of a patient with secondary amenorrhea, treated with 1,028,000 R.U. of  $\alpha$ -estradiol benzoate in oil intramuscularly, 860,400 R.U. of  $\alpha$ -estradiol orally, and 120 mg. of progesterone, over a period of approximately fourteen months, without causing uterine bleeding. Suction curettage following the hormone therapy, revealed atrophy of the endometrium and tuberculous endometritis. Attention is drawn to the possibility of disease of the endometrium, such as tuberculosis, causing amenorrhea by impairing the normal proliferative capacity of the endometrial tissue. The suggestion is made that an endometrial biopsy be done in all cases of functional amenorrhea before the institution of treatment; the biopsy should be repeated if bleeding does not occur after adequate hormone therapy.

*Treatment of Inguinal Hernia by Injection under Operative Visualization.* E. E. ARNHEIM AND H. NEUFELD. *Surgery* 10: 642, October 1941.

Injections under operative visualization were used in the treatment of direct and recurrent inguinal hernias and in conjunction with hernioplasties in combined indirect and direct inguinal hernias. Large amounts of psyllium seed extract were injected into the properitoneal tissues over the hernial sacs and between the transversalis fascia and the adjacent sacs. Trusses were worn in most cases following injections. Although injections under operative visualization have cured cases of inguinal hernia not suitable for cure by operation, the method has proved to be too uncertain in results to be advocated as a dependable therapeutic procedure.

*Results in Ninety Consecutive Thoracoplasties for Pulmonary Tuberculosis.* A. H. AUFSER. *J. Thor. Surg.* 11: 98, October 1941.

The results of 192 thoracoplasties performed on 90 consecutive patients at the Montefiore Hospital for Chronic Diseases from January 1, 1935, to July 1, 1940, were analyzed. An

upper selective thoracoplasty with complete removal of the first three ribs was the type of operation used. In 37 cases a Semb extrafascial apicolysis was added at the first stage. In 9 cases a one-stage procedure was all that was necessary for a good result. Nitrous oxide and oxygen anesthesia was used in most cases. Cyclopropane anesthesia was occasionally employed.

The end results are based on a 100 per cent follow-up study of from one to six years duration. There were 71 per cent arrested cases; 18 per cent not arrested; 7 per cent postoperative deaths, and 4 per cent late deaths. The classification "arrested" was used in conformity with the standards set by the National Tuberculosis Association. Of 43 cases operated upon before January 1, 1939, and discharged as arrested, 41 are working full time or doing housework; one patient is able to work but is unemployed and one is unable to work. Fifty per cent of the postoperative deaths occurred in patients over 40 years of age. Two of these were due to pneumonia and one was due to a transfusion reaction. One death was due to a phlegmon of the back, one to a pheochromocytoma of the adrenal and the last to a contralateral spontaneous pneumothorax.

In six cases the cause of failure was long standing disease with markedly fibrotic lung containing numerous small cavities. In five cases prolonged delay between the first and second stages appeared to be the reason for a poor end-result.

*The Present Status of the Surgical Treatment of Carcinoma of the Thoracic Esophagus.* J. H.

GARLOCK. *Am. J. Surg.* 54: 262, October 1941.

The author relates his experience with the surgical treatment of 54 cases of carcinoma of the esophagus and cardia. In 30 instances of squamous cell carcinoma of the esophagus, the operability rate was 63.3 per cent. The operative mortality was 42 per cent. In a group of 24 cases of adenocarcinoma of the cardia the operability rate was 37.5 per cent, and the operative mortality was 44.4 per cent. In both groups there are ten patients alive and well for periods ranging from five months to six years.

*Abdominal Pain in Cyclic Vomiting.* S. KARELITZ AND S. BLUMENTHAL. *Surgery* 10: 613, October 1941.

Cyclic vomiting in children is often associated with severe abdominal pain. The resemblance of the attack to acute appendicitis may be confusing. Children who are subject to bouts of cyclic vomiting may at any time be afflicted with acute appendicitis. On the other hand, if vomiting is protracted during an attack of appendicitis, evidences of ketosis may appear.

Differentiation between the two conditions is difficult but obviously necessary. One clue to the situation is the response to anti-ketogenic therapy.

In cases of cyclic vomiting with abdominal pain not caused by appendicitis, the pain subsides, vomiting stops, temperature falls to normal, and the pulse rate slows after the intravenous injections of glucose and saline. In those patients in whom appendicitis is responsible for vomiting sufficient to give rise to ketosis, injections of sugar and salt do not modify the pain, vomiting, fever, or tachycardia, although the metabolic disturbance is corrected. In fact in such patients the symptoms of appendicitis, masked by evidences of metabolic derangement, become clearer, assuring a more certain diagnosis.

Aside from the therapeutic test, a comparison of the clinical patterns of the two conditions yields reassuring confirmatory evidence.

The most effective form of treatment is the continuous intravenous instillation of 5 per cent glucose in Ringer's or Hartman's solution for one to three hours or longer, if necessary. This procedure controls acidosis, supplies fluid, avoids shock and provides sugar for the liver presumably depleted of glycogen. If operation is finally determined upon, such treatment constitutes excellent preliminary preparation.

*Anogenital Pruritus in Male Climacteric: Treatment with Testosterone Propionate.* R.

TURELL. *J. Clin. Endocrinol.* 1: 851, October 1941.

The author reported two cases of circumanal and perineal pruritus occurring in men of the

climacteric age, which was successfully treated by the administration of testosterone propionate. Therapeutically, the androgens in the absence of other therapy, were as effective in these patients as the estrogens are in the treatment of genital pruritus of menopause of some women.

*Cerebral Arteriography with Diodrast, Fifty Per Cent.* S. W. GROSS. *Radiology* 37: 487, October 1941.

Visualization of the cerebral circulation by means of the injection of a radio-opaque substance into the carotid artery was introduced by Moniz of Lisbon in 1927. The neglect of this procedure, which is known as cerebral angiography, was due to the objections and potential dangers of colloidal thorium dioxide, the substance advocated by Moniz. The author carried out experiments which consisted of injecting diodrast (3,4-diiodo-4-pyridon-N-acetic acid diethanolamine) into the carotid arteries of dogs. This substance is rapidly excreted by the kidneys and it is relatively nontoxic in the quantities used except for persons who have an idiosyncrasy for iodine compounds. Cerebral arteriography was then carried out in human beings with various concentrations of diodrast. A 50 per cent solution was found to be the most satisfactory. The procedure consists of exposing the common carotid artery under local anesthesia and injecting 12 to 15 cubic centimeters of diodrast solution by means of a curved 17-gauge needle. An x-ray film, previously placed in proper position, is rapidly exposed during the injection. Reactions can be avoided by the administration of 5 grains of sodium phenobarbital intramuscularly 15 minutes before the carotid artery is injected.

*Infantile Amaurotic Family Idiocy: Its Relation to Niemann-Pick Disease And Other Disturbances of Lipoid Metabolism; Report of Two Cases of Tay-Sachs Disease With Necropsy.* J. L. ROTHSTEIN AND SARA WELT. *Am. J. Dis. Child.* 62: 801, October 1941.

Amaurotic family idiocy (Tay-Sachs disease), a well defined clinical syndrome of morbid heredity, consists of idiocy associated with blindness. It results from an endogenous disease process, familial in character and always steadily progressive toward a fatal outcome. In recent years this disease process has come to be regarded as an expression of an underlying disturbance in the lipid metabolism of the nerve cell, and a close relationship has been postulated between amaurotic family idiocy and other diseases due to the disturbance of lipid metabolism, such as the Niemann-Pick syndrome and Gaucher's disease.

In this paper, the types of amaurotic family idiocy are divided into four groups. One group, the infantile form (Tay-Sachs disease) and Niemann-Pick disease are considered in detail as two types of syndromes resulting from disturbances of lipid metabolism and their possible relation is discussed. Two cases of infantile amaurotic family idiocy are reported from Dr. Schick's service. The pertinent necropsy findings are given in detail; the neuro-histopathologic observations of Dr. Joseph H. Globus in these two cases are presented and five photomicrographs loaned by him are included.

The main diseases resulting from disturbance of lipid metabolism are outlined (amaurotic family idiocy, Niemann-Pick disease, Gaucher's disease, Schüller-Christian disease, xanthomatosis and other forms of lipoidosis). The points of interest and of main significance are presented for comparison in tabular form.

*Werner's Syndrome: Report of the First Necropsy and of Findings in a New Case.* B. S. OPPENHEIMER AND V. H. KUGEL. *Am. J. M. Sc.* 202: 629, November 1941.

Werner's syndrome is a rare heredofamilial disorder characterized by sclero-poikiloderma, canities, premature baldness, precocious cataracts, endocrine stigmatization, changes in the larynx and voice, osteoporosis, metastatic calcification and constitutional physical inferiority. This report includes the only three cases observed in America; some twenty-five European instances have been recorded, but without post-mortem examination. The clinical evidence of endocrine stigmatization was confirmed by the following necropsy findings: atrophy of the testes and prostate gland, adenomata of the thyroid and adrenal, and evidences of hyperactivity of the parathyroid. The pituitary gland

showed no abnormality. The clinical evidences of parathyroid hyperactivity, including the results of the Hamilton test for excess of circulatory parathormone, are enumerated and their relation to the post-mortem findings are discussed.

*Trichophytin. II. Apparent Separation of Skin-Reactive Factor From Therapeutic Principle in Trichophytin.* S. M. PECK. Arch. Dermat. & Syph. 44: 816, November 1941.

We were able to prepare trichophytin fractions in which no skin test principle could be demonstrated even in persons who were strongly sensitive to the Lederle trichophytin. Such trichophytins were shown to be extremely effective in producing rapid desensitization in suitable patients without any local or focal reactions.

The experiments cited suggest that skin test factor is not necessarily identical with the desensitizing principle. Apparently some separation of one of these two factors has been accomplished.

*Multiple Exposure Technique in Contrast Visualization of Cardiac Chambers and Great Vessels.* M. L. SUSSMAN, M. F. STEINBERG, AND A. GRISHMAN. Am. J. Roentgenol. 46: 745, November 1941.

Our apparatus consists of either a Robot camera or a Leica camera with a Leica-motor which rotates a new section of film into position automatically after each exposure. This permits exposures to be made with ease every half second. Using an f 2.0 lens, in the average case, roentgen exposures of 0.3 second are used while the camera shutter is set at 0.5 second. Both mechanisms are released simultaneously. A Patterson B fluoroscopic screen and Agfa fluorapid film are used. The roentgenologic factors are 85 kv. (single phase), 150 ma., roentgen tube-screen distance, 27 inches. Using an f 1.5 lens, exposures of 0.2 second ordinarily suffice. A rotating target tube is essential for sharp detail. With this arrangement a minimum of ten exposures can be made during an eight second period of observation.

*Chancroid: Treatment with Sulfathiazole and Sulfanilamide.* B. N. KORNBLITH, A. JACOBY, AND L. CHARGIN. J. A. M. A. 117: 2150, December 1941.

A series of 175 consecutive ambulatory patients with chancroid infection were treated with sulfanilamide and sulfathiazole. Sulfanilamide was administered orally to 150 patients for 14 days; a total of 45.6 gm. in divided doses was found adequate. Sulfathiazole was administered orally to 25 patients for ten days; a total of 20 gm. in divided doses sufficed. All cases healed following oral chemotherapy in an average period of two weeks. Where the powdered drug was used alone, recurrences were observed. The intradermal reaction to Ducrey vaccine proved to be specific and was found positive in about 95 per cent of the cases.

*The Tuberculin Test. Comparative Results of the Intradermal and the Patch Test for One Thousand Patients.* H. A. REISMAN, AND M. GROZIN. Am. J. Dis. Child. 62: 1197-1204, December 1941.

The name Tuberculin Patch Test was given by Grozin to a method of testing for tuberculosis by the application of tuberculin and adhesive plaster to the intact skin, which if the reaction is positive results in an inflammatory area of reaction studded with small confluent papules and vesicles.

The advantages pointed out for this test were as follows: 1) It is painless and therefore does not frighten the child or spoil the good relationship between physician and patient. This is especially important in testing a resisting child. 2) It requires no boring, puncturing, scratching or rubbing of the skin. 3) It does not necessitate the use of syringes and needles (as in the Mantoux test) or of lancets or borers (as in the Pirquet test). 4) There are no instruments to sterilize. 5) There is no danger of infection. 6) There is considerably less risk attached to this test than to the intradermal method, which may give rise to necrosis, vesiculation and ulceration, especially in Negro children. 7) There is no fear of a general or focal reaction. 8) The technic is simple and is therefore especially

adapted to use by those who are not accustomed to making intracutaneous tests. 9) It saves time, particularly when large numbers of children are to be tested. 10) It is possible to control the size of the area of reaction, since it is limited to the surface covered by the adhesive tape.

The recognition of these advantages has in recent years led to development of commercial materials for performing tuberculin patch tests as well as to publication of a vast amount of literature on this subject.

Most recent publications on this subject deal exclusively with results obtained with commercial products. There is no need for further studies and evaluation of the non-commercial tuberculin patch test. With this aim in view, this test was performed routinely with a non-commercial preparation on 1,000 consecutive patients. For comparison, a Mantoux test was done simultaneously in all cases.

There was little disagreement between the results of the Mantoux test and of the tuberculin patch test. Only in 3 cases was the reaction positive to the intradermal and negative to the patch test. In 2 cases the reaction was negative to the Mantoux test and positive to the patch test.

The testing material used was Koch's old tuberculin, supplied in vials by the Bureau of Laboratories of the New York Department of Health.

There were no unfavorable reactions from the tuberculin patch test in our series, although there was mild itching in some cases. The usual changes were the production of hyperemia followed by the formation of papules and tiny vesicles, limited to the area of the skin in contact with the tuberculin. After the removal of the adhesive tape any reaction due to it disappears twelve to twenty-four hours later, while that due to the tuberculin becomes more distinct. It is therefore advisable to interpret the results one to two days after removing the adhesive tape. If the reaction to the tuberculin patch test is negative and there is still a suspicion of tuberculosis, the next procedure should be a Mantoux test done with a 1:100 dilution of old tuberculin.

The non-commercial tuberculin patch test is reliable and compares favorably with the intradermal (Mantoux) test performed with 0.1 mg. of a 1:1,000 dilution of old tuberculin.

## BOOK REVIEWS

*Diseases of the Gastro-Intestinal Tract.* ASHER WINKELSTEIN, M.D. New York, Oxford University Press, 1942.

This book embodies in outline form an extensive experience in gastroenterology over a period of twenty years. It is the outgrowth of post-graduate lectures given at The Mount Sinai Hospital during that period. While written in concise form it is noteworthy to find that the important gastro-intestinal diseases are presented in a very complete manner.

The book is intensely practical and even includes detailed instructions for drug and dietetic therapy. Although intended chiefly for medical students and busy practitioners, it also contains much that is of great interest for the specialist. Dr. Winkelstein has included his own contributions to gastroenterology. There is a description of the intra-gastric drip therapy for peptic ulcer, the antitoxic B. coli serum therapy for ulcerative colitis and the syndrome of peptic esophagitis. Of particular value are the chapters dealing with chronic gastritis, peptic ulcer, ulcerative colitis and regional ileitis. This book may be highly recommended for its clarity, judicious approach and its great practical value.

A. C.

*Understand Your Ulcer. A Manual for the Ulcer Patient.* BURRILL B. CROHN, M.D., F.A.C.P., New York, Sheridan House, 1943.

This book represents another effort to teach the lay population medicine, and meets one of the crying needs of modern medicine. In professional relations between doctor and patient it is essential that the doctor be a teacher as well as a healer. The work is not intended to replace the physician but only as an orientation in this disease. The work is particularly timely because the incidence of ulcer seems to have increased not only in the past decade, but more particularly in the present war, as the appalling rejections and discharges of recruits in the armies eloquently testify. Dr. Crohn has performed a most praiseworthy job. His language is such that the average layman may readily understand, he has handled controversial aspects judiciously and his exposition is clear and logical. Particularly praiseworthy is Dr. Crohn's emphasis on the psychosomatic aspects of the ulcer problem. About a third of the final portion of the book is a valuable appendix on diet written by Sylvia Bayard. The illustrations are mostly diagrammatic and well express the spirit of the book.

E. M.



PHARMACOLOGY AND TOXICOLOGY OF SULFONAMIDES<sup>1</sup>

ERNEST P. PICK, M.D.

## PHARMACOLOGY

I. *Sulfonamide*, the basic compound from which, up to the present, over thirteen hundred synthetic derivatives have been produced, was first synthesized in 1908 at the Vienna Technical Institute by Gelmo. Although this substance had been used in combination with azo-dyes its antibacterial properties had, on the whole, remained unknown. Not until 1927 was this work revived by Gerhard Domagk, who became interested in these substances through Hörlein, who at that time was Director of Research at the I. G. Dye Research Institute in Löwerkusen. Five years later Domagk, using a synthetic azo-dye compound, *sulfamido-chrysoidin* (Prontosil) synthesized by Mietzsch and Klarer, was able to demonstrate that mice could be protected against otherwise fatal hemolytic streptococci infections by the administration of this compound. Domagk (17) first published these observations in 1935, and in 1936 Long and Bliss (2) in this country reported on the chemotherapeutic properties of sulfonamides, thus establishing the basis for the greatest progress in the therapy of infectious diseases since Ehrlich's salvarsan therapy for syphilis.

The investigation of these compounds, however, has another biologic importance; these aromatic amino-sulfo-compounds appear to throw light upon certain of the most intricate enzymatic processes in cells. A most significant observation was that the most important property of these substances was not their bacteriocidal action, but rather their inhibitory effect on growth of micro-organisms, the so-called *bacteriostatic effect* exerting a delaying or inhibiting action upon the multiplication of micro-organisms. This takes place without any increase in the defensive powers of the body, such as the natural immunologic mechanisms, with the formation of antibodies and immune substances remaining apparently unaffected. Bacteriostasis does not occur immediately on placing the organisms in contact with the drug; it takes place only after a variable period of time, 2 to 5 hours, after a so-called "lagphase." This "lagphase" in the action of sulfonamides is noted *in vitro* and *in vivo*. It is suggested that it is due to the gradual exhaustion of an organic substance required by growth, an "essential metabolite" which cannot be synthesized by the micro-organisms in the presence of sulfonamides and manifests itself by cessation of cell division.

The pharmacologic action of these substances is definitely associated with the growth stimulating and inhibiting processes of micro-organisms. Fildes (18) in 1940 suggested that the entire bacterial action of sulfonamides of inhibiting bacterial growth is attributable to the interference with the action of an essential metabolite without which bacterial metabolism cannot proceed to the

<sup>1</sup> Lecture delivered on March 29, 1943 at the monthly Conference of the New York Institute of Clinical Oral Pathology at the New York Academy of Medicine.

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extent required by growth, in a sense therefore interpreted as a mechanism of "enzyme blockage." Further important progress was reported by Rubbo and Gillespie (23), then Park and Wood (20), who found interestingly enough that *para-amino-benzoic acid* is an essential metabolite, having a marked stimulating effect upon the growth of *clostridium-acetobutyricum*, while the same compound exerts a specifically inhibiting effect upon the bacteriostatic action of sulfonamides. Meanwhile other metabolites were found essential for the growth of micro-organisms. Among such various metabolites are other cleavage products of proteins, as for example, peptones, tryptophane, indol, methionate, then vitamins, such as nicotinic and pantothenic acids, biotin, Folic acid, etc. (8). The essential metabolite, however, which appears to be most important for the growth of micro-organisms seems to be *para-amino-benzoic acid*, which is simultaneously the specific inhibitor of the action of sulfa drugs *in vitro* and *in vivo* (22). This bacteriostatic effect of sulfa drugs may be selectively blocked by a sufficient concentration of such metabolites. Therefore it can be readily concluded that only an effective concentration of sulfa drugs in the blood is able to overcome the action of inhibitor substances and to achieve a sufficient degree of bacteriostasis, thus leading to the bacteriocidal effect by the natural defensive powers of the body. Thus, it is understandable that sulfonamides may be ineffective when introduced into abscess cavities, in which, as a result of autolytic and enzymatic processes, inhibitory protein-products such as peptone and amino acids are produced. It should be borne in mind, however, that the more powerful agents such as sulfapyridine or sulfathiazole are bacteriostatic in the presence of amounts of inhibitor which completely annul the action of sulfanilamide. Furthermore, it is to be noted that sulfa drugs act to some extent against certain bacterial toxins (9). The inhibitor action of *para-amino-benzoic acid* seems likewise to interfere with this detoxifying effect.

The discovery of essential factors which inhibit the bacteriostatic action of sulfonamides, led to an understanding of so-called *bacterial resistance* which is of clinical importance. This bacterial resistance can be developed in various micro-organisms under the influence of *inadequate* amounts of sulfa drugs *in vivo* and *in vitro*. Intensive studies up to the present have failed to disclose significant differences in morphology, growth rate, carbohydrate fermentation, virulence, etc. between sulfonamide-resistant and susceptible organisms. MacLeod (12) showed in one fast strain of pneumococcus an increase in the production of hydrogen peroxide and a decrease of dehydrogenase activity toward glycerol, both lactate and pyruvate and at the same time an increased production of a substance inhibitory to the bacteriostatic action of drugs. Recently, however, Landy and his associates (26), have found that sulfonamide-resistant strains of *staphylococcus aureus* produce greater amounts of *para-amino-benzoic acid* than their parent strains. It is evident that the quantity of *para-amino-benzoic acid* synthesized by resistant strains appears sufficient to explain the phenomena of sulfonamide-fastness in *staphylococcus aureus*. Former studies of Mirick (21) yielded similar results; a drug-resistant pneumococcus synthesized ten times as much *para-amino-benzoic acid* as its parent strain.

It is quite possible that other micro-organisms which acquire resistance to sulfonamides without showing an increased production of para-amino-benzoic-acid produce other as yet unidentified "anti-sulfonamide metabolites". It is significant to note that Kirby and Rantz (23a) observed that organisms which were resistant to certain bacteriostatic concentrations of one sulfa drug were equally resistant to similar bacteriostatic concentration of other sulfonamides. Fastness seems to be directly proportional to the relative bacteriostatic potency of the drugs and their molar concentration (MacLeod (12)).

II. The clarification of certain general pharmacologic properties of sulfonamides calls for the consideration of some chemical structural formulas: Of all sulfa drugs the sulfanilamido group seems to be the most effective grouping.

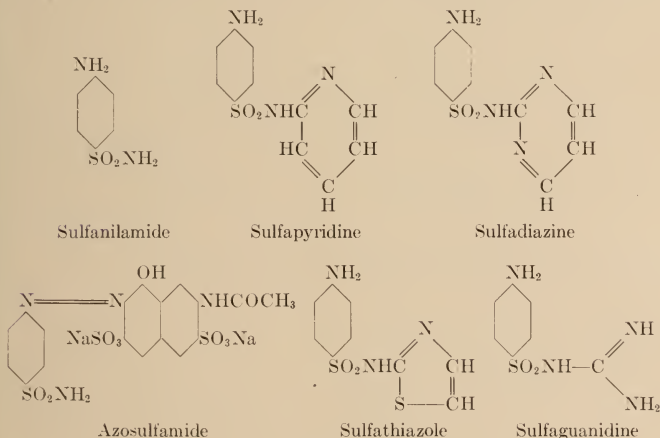


FIG. 1

Here the paraposition of the amino group to the sulfamido groups is essential to therapeutic effect. All drugs now clinically used are the products of the substitution of hydrogen in the sulfamido group by pyridine (*Sulfapyridine*), by thiazole (*Sulfathiazole*), by pyrimidine (*Sulfadiazine*), by acetimide (*Sulfacetimide*) or by guanidine (*Sulfaguanidine*) (figs. 1-4).

The substitution of one hydrogen in the amino group occurs in the liver; here the sulfa drugs are conjugated with an *acetyl*- or with a *glycuronic*-group (13, 14). It is important to know that these acetylated or glycuronated products, which may be in the blood in colloidal solution are practically insoluble in urine, are deposited as crystals in the kidneys, and are eliminated with difficulty. These *acetyl* compounds are therapeutically ineffective and constitute a serious danger to the function of the kidneys, particularly with the prolonged use of larger doses

of slowly eliminated sulfa drugs and restricted water intake. A fluid intake of at least 3000 cc. of water daily and a urine output of 1400 cc. may avert renal disturbances; frequently, however, immediate discontinuation of the damaging drug may be required.

The administration of *alkalies* for the purpose of hindering the precipitation of crystalline acetyl compounds have not proven satisfactory when employed with the formerly much used sulfapyridine. Recent investigators demonstrated that the administration of alkali is of special benefit when given in con-

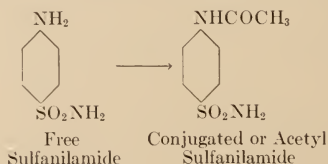
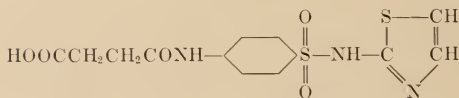
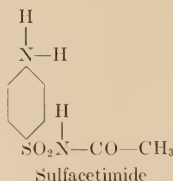


FIG. 2



Sulfasuxidine (Succinylsulfathiazole)

FIG. 3



Sulfacetimide

FIG. 4

junction with sulfadiazine or sulfathiazole since the sodium bicarbonate (10 to 20 Gm. daily) increases the urine-solubility of sulfadiazine-acetyl compounds two and one-half times (15, 27).

III. *The special pharmacological action* of sulfa drugs depends on their solubility, rate of absorption, excretion and on a satisfactory concentration of the *free* drug in the body. It should be mentioned here that according to Loughlin and his associates (28) the acid and sodium salts of Sulfapyridine, Sulfathiazole and Sulfadiazine are absorbed rapidly (five minutes after peroral administration) from the gastro-intestinal tract, presumably from the stomach. Even conjugated forms are present in the blood as early as five minutes following peroral

administration of these compounds (27). The most important facts concerning the clinical use of these drugs are shown, in accordance with statements by Long (2, 10, 25), Marshall (1, 33), Janeway (3), Brown (4) and others, in Tables I and II.

It must be noted here, however, that a previous view that the various sulfa drugs had a definite specific action upon certain pathogenic organisms, no longer receives general support; but rather it appears that the bacteriostatic action depends primarily upon the concentration of the *ionized drug*, namely that the active sulfonamide exists as an anion (Fox (19), Schmelkes (11), Cowles (11a)). This would explain the various bacteriostatic powers of different sulfa drugs against one especially sensitive organism *in vivo*, namely, against gonococci, but also against one less sensitive organism as the tubercle bacillus. This antibacterial activity of the sulfonamides for B. tuberculosis may also be correlated with their acid dissociation constants (32).

a) *Sulfanilamide (Prontiline)* despite subjective discomforts, e.g., nausea, vomiting, and frequently cyanosis, acidosis and hemolytic anemia is the drug of choice in the treatment of infections with hemolytic streptococci and a second choice with meningococci. It produces renal complications very rarely and is the only sulfa-drug used for the treatment of hemorrhagic nephritis. Sulfanilamide is not effective against staphylococci or pneumococci. Sulfadiazine is a close second choice in the treatment of infections produced by hemolytic streptococci and meningococci.

*Azotsulfamide (Neoprontosil)* has the same properties as sulfanilamide because the whole effect of this drug is produced by splitting off the sulfanilamide compound.

b) *Sulfapyridine (Dagenan)* is especially effective against pneumococcal pneumonia and is the only sulfa drug with antipyretic action (13). This however, is not a reliable criterion for control of infection. This drug with its irregular absorption producing nausea and vomiting and renal complications has been nearly replaced by sulfathiazole and sulfadiazine.

c) *Sulfathiazole* is a powerful and polyvalent agent and it is the drug of choice for urinary infections by Coli bacilli, gonococci, staphylococci, gas gangrene and anthrax. Its *rapid excretion* causes difficulties in maintaining the desired blood level. Although this drug does not always provoke subjective discomfort, it may be *very toxic*. Hypersensitivity with fever and severe intoxication-symptoms with miliary necrosis in various tissues and organs or lesions in the myocardium, kidneys, brain (similar to arsphenamin intoxication) may occur with rather small doses (6a).

*Sulfathiazole* is better absorbed than other drug from the peritoneal cavity and seems to be the drug of choice for intraperitoneal local use. Conjugated with succinic acid (*succinyl-sulfathiazole*) this drug is highly effective in the local treatment of coliform infections localized in the intestines because of comparatively little absorption in the large intestine (4, 16, 27).

d) *Sulfadiazine* with low toxicity, without provocation of nausea is in general the drug of choice in therapy of various types of infections. It may be adminis-

tered orally, intraperitoneally and locally; it has a lower toxicity than other sulfonamides (27). It is superior to sulfathiazole in pneumococci infections and to sulfanilamide in meningococci-meningitis when the treatment must be continued for more than ten days. For staphylococci infections, however, sulfathiazole is preferred. Because of very slow excretion a high blood level is achieved early. To avoid delayed severe toxic reactions in the kidneys, non-protein nitrogen in the blood, leucocytes, further water intake and urine output must be checked cautiously. Stopping the drug and forcing fluids together with administration of sodium-bicarbonate is the method for averting toxic reaction.

e) *Sulfaguanidine* being quite water soluble is absorbed poorly from the bowel. However, high concentrations may be achieved in the intestinal tract while the concentration in the blood remains low. It should be effective in acute bacillary dysentery (33).

TABLE I  
*Some properties of sulfa drugs*

DRUG	H <sub>2</sub> O SOLUBILITY	ABSORPTION	EXCRETION	DESIRED BLOOD LEVEL IN MG. %
Azosulfamide (Neoprontosil) . . . . .	5%	rapid	rapid	8-15
Sulfanilamide (Prontiline) . . . . .	1%	rapid	rapid	8-15
Sulfapyridine (Dagenan) . . . . .	0.03%	irregular	mod. rapid	5-10
Sulfathiazole . . . . .	0.1%	rapid	very rapid	3-7
Sulfadiazine . . . . .	0.01%	fairly slow	slow	8-15
Sulfacetimide (Albucid) . . . . .	1.0%	rapid	rapid	4-5
Sulfaguanidine . . . . .	0.2%	poor	good	2-5
Succinyl Sulfathiazole . . . . .		poor	good	

f) The properties of *Sulfacetimide* (*Albucid*) are shown in Tables I and II. This drug is rapidly absorbed and eliminated from the blood and excreted by the kidneys largely unchanged. It is indicated for the treatment of urinary infections especially for those with *B. coli* and gonococci. Sulfathiazole, however, seems to be more effective.

IV. *Dosage*: For severe infections all sulfa drugs may be administered orally, 4-6 Gm. in divided doses for the first two days, for milder infections (as of the urinary tract) 2-3 Gm. daily in divided doses for 10 to 12 days. For intravenous use sodium sulfadiazine 5 per cent solution in distilled water or in saline has a great advantage over sodium sulfathiazole because of its slower excretion. For subcutaneous administration only 0.5-1-2 per cent solutions are indicated; stronger concentrations are very dangerous because of the alkalinity of these sodium salts. Sulfanilamide in 1 per cent solution may be used because it is rapidly absorbed. Other slowly absorbed drugs lead to an accumulation in the blood after repeated doses. Crystalline sulfanilamide 0.05-0.1 Gm. per square inch equivalent to two and one-half centimeters of wound surface is recommended for local treatment of wounds; a synergistic effect has been shown when

applied with azochloramide solution in 1:3300 in dressings, which is effective in neutralizing the action of the sulfa drug inhibitors (16).

#### TOXICOLOGY.

It is evident that substances like the sulfonamides, which can go into combination with numerous metabolites in the body can as well produce toxic reactions and metabolic disorders in various organs. So, for example, it is note-

TABLE II  
*Some properties of sulfa drugs*

DRUG	ACETYLATION IN % OF TOTAL AMT.	TOXICITY	RENAL COMPLICATIONS	PRINCIPAL BACTERIOSTATIC EFFECT
Azosulfamide (Neopronto- sil)	Slight (10-15)	Mild	Very rare	Hemolytic streptococci Meningococci Actinomycosis Gas gangrene
Sulfanilamide (Prontiline)	Slight (10-15)	Mild (naus.- vom.)	Very rare	Lymphopathia venereum
Sulfapyridine (Dagcanan)	Great (15-75)	Mild (naus.- vom.)	Hematuria freq.	Pneumococci Meningococci
Sulfathiazole	Slight (10-30)	Toxic (naus.- vom.)	Oliguria and Hematuria	Staphylococci Coli bacilli Gonococci
Sulfadiazine	Slight (10-30)	Low	Oligura and Hematuria	Pneumococci Meningococci Staphylococci-meningitis
Sulfacetimide (Albucid)	Slight	Mild	Oligura occas.	Gonococci Urinary infection Coli bacilli
Sulfaguanidine	Moderate	Mild		Bacillary dysentery
Succinyl Sul- fathiazole	Moderate	Mild		Coli bacilli

worthy that even the administration of small amounts of many of these compounds can result in marked nutritional disorders in small experimental animals. Sebrell and his co-workers (6) showed that a diet containing only 1 per cent of sulfaguanidine or sulfasuxidine is able to inhibit the growth of rats, perhaps by means of lowering the intestinal synthesis of essential growth factors; further to produce Biotin-vitamin K and Folic acid-deficiency (29) in purified diets.

Among the toxic effects observed in the human body we must especially differentiate: 1) effects upon the central nervous system; 2) effects upon thermo-regulation; 3) effects upon the blood picture; 4) organic damage to liver and kidneys; and 5) skin changes.

1) Among the toxic effects upon the central nervous system commonly noted in humans are anorexia, nausea and vomiting. These symptoms seem to be caused by yet unknown disturbances in metabolism of the central nervous system and are not due to gastric irritation. Large doses of sulfonamides cause convulsions and spasticity in animals, an indication of the action of sulfa drugs on the central nervous system. It may be that other parts of the nervous system are also injured by these drugs. An important practical point mentioned by Jane-way (3) is that ambulatory patients taking sulfonamides may show a slowed reaction time, thus making it necessary that special care should be observed by these persons in driving a car, crossing the street or performing manual work. Vertigo, lack of coordination, mental lapses and various other motor and psychic disturbances are commonly observed in the course of sulfanilamide and sulfapyridine administration, but are less frequent with sulfathiazole and especially with sulfadiazine. In this connection it must be further pointed out that the preliminary treatment with sulfa drugs leads to a considerable increase in the toxicity of papaverine, codeine, morphine, barbiturates and novocaine-adrenalin mixtures (5). In this respect the newest investigations of S. Glaubach (24) are of interest: they demonstrate that the brains of mice which have been pre-treated with sulfapyridine possess an increased permeability to methylene blue. This phenomenon may be perhaps one of the factors producing an increased susceptibility of sulfa drug-treated animals to alkaloids and narcotics.

2) Other important, and perhaps one of the commonest reactions observed, is "drug-fever". The mechanism of this phenomenon is at present not understood, and may occur without accompanying rash, arthralgia or lymphadenopathy. This condition seems to result from individual sensitization to the drug, despite the fact that up to this time no one has been able to find specific antibodies in patients with such a hypersensitivity. Attempts were made to transfer hypersensitivity passively with serums, but were entirely unsuccessful. Sulfathiazole appears to be the greatest offender in this regard while sulfadiazine is the least, according to Long (25). It is perhaps interesting to note that sulfapyridine sometimes markedly depresses fever; this action, however, cannot be attributed to the bacterial-therapeutic effect of this drug (14a).

3) All sulfonamides may produce blood disorders of almost any type. Hemolytic anemia with hemoglobinuria is quite commonly a complication of sulfanilamide and sulfapyridine administration, but is apparently not associated with any permanent damage if treatment is discontinued before the anemia becomes severe. The anemia, however, tends to recur in about two-thirds of the susceptible patients if the drug is repeated a second time. Sulfathiazole or sulfadiazine rarely produce this type of toxic reaction.

Sulfonamide-cyanosis seems to be due to a combination of methemoglobin and colored oxidation product formation of sulfanilamide; this cyanosis is not actually harmful and may be reversed by the reducing action of methylene blue (0.065 to 0.13 Gm. every hour orally, or 1 to 2 mg. per kg. intravenously) (34, 35). This condition may be of significance in aviation medicine because of the anoxia which could result from the formation of methemoglobin.

The most feared toxic complication is agranulocytosis because granulocytes are particularly susceptible and agranulocytosis or granulocytopenia therefore occur if treatment is continued beyond the twelfth day. Sulfapyridine seems to be the drug most responsible for this type of toxicity which is rarely encountered in the administration of sulfathiazole or sulfadiazine. Leucopenia and thrombocytopenia with accompanying purpura may result from the use of all these drugs but it is to be noted that the latter is a rare toxic reaction.

Of high interest are some experimental investigations showing the importance of B-vitamins in the development and treatment of these blood-dyscrasias. Sebrell and his associates (6) produced in rats receiving purified diets into which 1 per cent of sulfaguanidine or sulfasuccidine were incorporated agranulocytosis, granulocytopenia, leucopenia and hypocellularity of bone marrow. These blood dyscrasias are perhaps connected with biotin deficiency and can be prevented or successfully treated with liver preparations. Besides these blood abnormalities there occurred in such animals hyaline sclerosis and calcification of blood vessels. C. A. Elvehjem (29) reports to be able to develop in rats following treatment with certain sulfa drugs blood disorders (white blood cell anemia) produced probably by lack of Folic acid, one of the newest B-vitamins; thus, this anemia can be prevented by Folic acid.

4) Of great interest also is the *visceral damage* usually associated with damage to the circulatory apparatus. It must be emphasized that especially two organs are involved here, the liver and kidneys. Liver damage has been responsible for a number of fatalities in which the pathology was similar to that found in acute yellow atrophy of the liver. Enlargement of liver, spleen and axillary lymph nodes is a common and early sign of intolerance in the treatment of gonorrhea with sulfapyridine (30).

The kidneys may be damaged twofold: First by blockage of the kidney tubules and pelvis or ureters with precipitated acetylated sulfo-compounds or secondly by the development of a true toxic nephritis simulating the nephrosis of mercury bichloride poisoning. This may result especially from sulfathiazole administration even with rather small doses. This sulfathiazole poisoning seems to be the *most dangerous type* because it is sometimes associated with myocardial lesions, encephalopathy (hemorrhagic type of encephalitis) and with multiple small nodules of miliary necrosis in the various tissues. An explanation of this severe and frequently fatal poisoning still remains to be found (6a). Hematuria is of importance when administering sulfapyridine, sulfathiazole, and sulfadiazine; at this point it should be noted that the greatest advantage of sulfanilamide therapy is the rare occurrence of renal complications.

A remarkable observation is the thyroid hyperplasia in rats which occurs under influence of various sulfa drugs; that is considered to be compensatory to the failure of thyroid hormone synthesis (31).

5) *Skin manifestations* of various types may occur, frequently accompanied by fever, lymphadenopathy, splenomegaly, and arthralgia. These symptoms are comparable in some instances to serum sickness. Sulfathiazole is again the most frequent cause of these complications and sulfadiazine the least. Photo-

sensitization may develop during sulfonamide therapy and it is therefore important to instruct patients to avoid direct rays of the sun and ultra-violet radiation. Usually these complications are mild and harmless, but occasionally there may occur a fatal pemphigus even though the drug has been stopped. Dermatitis produced experimentally in rats given sulfaguanidine or sulfasuxidine is cured by Biotin as was shown by Spicer, Daft, Ashburn and Sebrell (6).

Dowling and Lepper (7) reported recently toxic reactions following therapy with sulfapyridine, sulfathiazole and sulfadiazine; they have found toxic effects in 29.9 per cent of 498 patients treated with sulfapyridine, 11.8 per cent of 321 patients treated with sulfathiazole and 7.7 per cent treated with sulfadiazine. The optimal therapy for most infectious diseases at the present time involves the use of sulfadiazine according to these authors. The only death in the entire series occurred in a patient with acute hemolytic anemia following sulfapyridine therapy.

Long (25) reports that approximately five thousand deaths have been caused to date by sulfanilamide therapy. Most of these fatal toxic reactions were due to the development of agranulocytosis and acute hemolytic anemia. Though this mortality is not high in comparison to the great number of cases treated with sulfa drugs, he believes that these casualties could be considerably reduced by daily examination of all patients, "observing the urine output and making total white blood cell counts at frequent intervals; prompt withdrawal of the drug and the forcing of fluids at the first sign of trouble will result in most instances in prompt recovery from the toxic reaction."

The continuation of sulfonamide drug administration is justified despite moderate toxicity only in severe infections such as in cases of meningitis and bacteremia in which the prognosis ordinarily is poor. In mild illness such as gonorrhea and tonsillitis the continued use of sulfonamides despite marked symptoms of headache, vertigo, nausea, anorexia, rash and other signs may be sometimes very dangerous to the patient; these mild symptoms may frequently precede, as Brown (4) emphasized, more serious complications and require the discontinuance of sulfonamides.

You will recognize from this brief report that these excellent drugs, when in the hands of experienced physicians, contribute a great deal to the success of present therapy, but must always be used only with the greatest care.

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## RETROPERITONEAL TERATOID TUMORS IN INFANCY AND CHILDHOOD

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Retroperitoneal tumors form an important group of neoplasms in infancy and childhood. The two most common retroperitoneal tumors are neuroblastoma sympatheticum and embryoma of the kidney. Thus, in a group of 301 malignant tumors in childhood removed either at operation or at autopsy during the ten-year period ending September 1939, Farber (6) collected 32 cases of retroperitoneal neuroblastoma and 30 cases of embryoma of the kidney; in the same period, 1 retroperitoneal teratoid tumor was found. A recently observed case of retroperitoneal teratoid tumor in an infant led to a review of the literature of this unusual condition.

### CASE REPORT

*History* (Adm. 487980). A female infant, aged 3 months, was admitted to The Mount Sinai Hospital on April 8, 1942. The infant was born full-term, weighing 8 pounds and 2 ounces. An increase in the size of the abdomen was noted by the mother at the age of 6 weeks, the abdominal enlargement becoming progressively greater. The only other complaint was constipation.

*Examination.* The infant was well developed and well nourished, weighing 12 pounds and 2 ounces. The head was symmetrical in outline, the posterior fontanelle was closed, and the anterior fontanelle measured 2 cm. in diameter. There were no abnormalities of the eyes, ears, nose, and throat. Pea-sized lymph nodes were palpable in the cervical, axillary, and inguinal regions. The heart, lungs, extremities, and genitalia were normal. The deep reflexes were active and equal.

Dilated veins in the abdominal wall, filling from below upward, were noted. There was marked swelling of the abdomen with an obvious bulge in the left flank (fig. 1). This enlargement was produced by a huge mass which filled the left flank and the left side of the abdomen from the costal margin to the pelvis, with an extension of the mass into the right lower quadrant. The tumor was firm, elastic, and ballotable into the left lumbar region. Several walnut-sized hard masses were palpable in the right lower quadrant of the abdomen at a distance from the large tumor. The edge of the right lobe of the liver was felt at the costal margin. The spleen was not palpable. On rectal examination, a hard nodule was felt high on the right side.

*Laboratory data.* Urine: No abnormalities except for a slight trace of albumin. Blood: hemoglobin, 15.8 gm. per 100 cc.; red blood cells, 5,900,000; leucocytes, 16,100, of which there were 24 per cent polymorphonuclear leucocytes, 64 per cent lymphocytes, 6 per cent myelocytes, 3 per cent monocytes, 2 per cent eosinophiles, and 1 per cent basophiles. Blood urea nitrogen, 21 mg. per cent. Wassermann, Schick, Mantoux, and Brucella tests, negative.

Roentgen examination of the chest and long bones revealed no abnormalities. An x-ray film of the abdomen, without the use of contrast media, showed a large mass filling the left side and part of the right side of the abdomen; small areas of irregular opacification were noted on the right side just above the right iliac crest. An intravenous pyelogram (fig. 2) revealed the mass as noted in the film of the abdomen, with the intestines displaced to the right side of the abdomen. No abnormality was noted in the right upper urinary tract; the left kidney pelvis was only faintly visualized, but no gross abnormality in the

contour of the calyces was demonstrated. The right psoas margin was faintly outlined, and the left psoas margin was obliterated.

*Operation.* Under ether anesthesia, a long oblique incision was made, extending from the left flank across the left mid-abdomen to the right lower quadrant, dividing the left rectus and oblique musculature and a portion of the right rectus muscle.

A large tumor, filling most of the abdominal cavity, was found. The tumor measured about 6 inches in diameter, and was spherical in outline. The appearance and consistency of the tumor varied; much of it was cystic, its wall whitish in color and thick. In the lower solid portion of the tumor, areas of calcification were felt. The mass encroached upon the



FIG. 1. Preoperative photograph of the infant showing marked abdominal enlargement

entire length of the descending colon which overlay its left lateral surface. The left colic vessels were in close proximity, and in places adherent, to the wall of the tumor. The small intestines and a mobile cecum were compressed into the right lumbar gutter.

In order to reduce the size of the cystic portion of the tumor, a trocar and cannula were inserted into it and about 600 cc. of white mucoid fluid were aspirated. By sharp and blunt dissection, a plane of cleavage was established to the left of the tumor and developed just mesial to the colic vessels. At the areas of close attachment to the vessels, where dissection was more difficult and where the wall of the tumor was quite thick, some bleeding was encountered from branches of the left colic vessels. The third portion of the duodenum and the first loop of jejunum were adherent to the dome of the tumor, but these structures were separated from the mass without difficulty. The solid portion of the tumor, in its

lower right half, was relatively fixed posteriorly, but could be satisfactorily mobilized. When complete mobilization of the tumor on all sides had been performed, no fixed attachment posteriorly was found. After removal of the tumor, most of the lumbar retroperitoneal space, the aorta, the inferior vena cava, and the left kidney and ureter were exposed. There was no obvious bleeding from the retroperitoneal tissues. Two broad layers of the posterior peritoneum were then developed, extending from the ascending colon on the right to the descending colon on the left, from the third portion of the duodenum above to the iliac region below. These layers of peritoneum were approximated with interrupted sutures of fine silk.



FIG. 2. Roentgenogram of the abdomen and intravenous pyelogram showing the large mass filling most of the abdomen and displacing the intestines to the right side; areas of ossification in the tumor are visualized just above the right iliac crest.

The abdominal wall was closed in layers. A continuous 5-0 chromicized catgut suture was used for the peritoneum, and interrupted fine silk sutures for the oblique musculature, rectus sheath, and skin.

*Course.* An intravenous infusion of 5 per cent glucose in saline and citrated blood was administered throughout the operation; 100 cc. of blood were given during the operation and in the early postoperative hours. Additional transfusions of citrated blood were administered, 100 cc. on the first postoperative day, and 75 cc. on the second day; during this period the intravenous glucose-saline was continued. During the second and third postoperative days 2 grams of sulfathiazole were given. Feedings were started on the second day.

There were rises in temperature to 104°F. on the first postoperative day, 103°F. on the

second day, and 101.4°F. on the seventh day; the temperature was otherwise normal. Following mild shock during the first 48 hours after operation, the convalescence was uneventful. The dermal sutures were removed one week after operation. The wound healed by primary union except for a small area of superficial subcutaneous infection (fig. 3). The infant was discharged 17 days after operation, weighing 9 pounds and 10 ounces.

Examination on May 8, 1942, 1 month after operation, showed a gain of 6 ounces in weight and the general condition to be excellent. An additional gain in weight of 3 pounds was noted on June 8, 1942, 2 months after operation.



FIG. 3. Photograph of the abdomen showing the wound two weeks after operation



FIG. 4. Photograph of the tumor showing the cystic structure

*Report of pathology.* The specimen (fig. 4) was a cystic tumor which measured about 6 inches in diameter. The surface was nodular, in part smooth, and in part covered by membranous adhesions. Most of the surface was white in color, but there were some bluish nodules and areas of hemorrhage. The cystic portion of the tumor was made up of a large cyst and many smaller cysts; several daughter-cysts were found in the wall of the large cyst. One portion of the wall of the large cyst consisted of nerve tissue and cartilage. Bone was found in one of the daughter-cysts. The smaller solid portion of the tumor, in the bluish nodules, was made up of cartilage and nerve tissue.

On microscopic examination, representatives of the three embryonal layers were found. The mesodermal elements predominated as cartilage (fig. 5 B), bone, an immature tooth, smooth muscle, fat, and connective tissue. The structures of ectodermal origin were squamous epithelium which lined many of the cysts (fig. 5 A), sebaceous glands, and nerve tissue. Entodermal tissues were least frequent and were represented by columnar epithelium and goblet cells as seen in the large intestine, and columnar ciliated epithelium suggesting bronchial mucous membrane.

#### GENESIS AND PATHOLOGY

The classification of teratoid tumors is in a somewhat confused state. The following definition is useful (Williams (25)): A teratoma comprises easily recognizable fetal parts, more or less included in the tissues of the autosite; the term teratoid tumor refers to tumors containing derivatives of the blastodermic

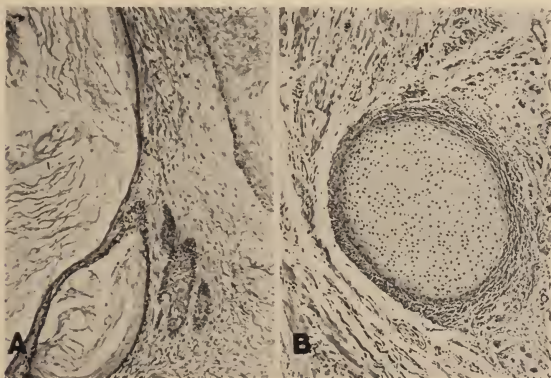


FIG. 5A. Sections of the tumor (photomicrograph,  $\times 200$ ) showing cyst wall lined by squamous epithelium; B. area of cartilage and smooth muscle.

layers without the formation of organs. These tumors are not homologous with the embryo, and they possess none of the characteristics essential for independent existence. They are attributed to descent from a totipotent germinal cell or blastomere. It has been assumed that these tumors are the result of an irregularity or malformation of the primitive streak, usually arising in the vicinity of the caudal or cephalic end of the developing body-axis, but their topographical distribution in post-embryonic life may be diverse. All the members of the intraabdominal group center about the vicinity of the primitive mesentery; they are always extraperitoneal, being in existence before the peritoneum is evolved.

Teratoid tumors contain representatives of the embryonal elements, ectoderm, entoderm, and mesoderm, in a disorderly arrangement. The less highly specialized somatic tissues are usually represented—the general mesenchyme, the

various forms of surface and duct epithelium, and simple glands. The most common derivatives of the ectoderm are the epithelium of the skin and its appendages, and elements of the nervous system in their less specialized forms. Of the entodermal derivatives, the respiratory and alimentary systems are usually represented in their simplest forms as bronchial and intestinal mucous membranes. Derivatives of the general mesenchyme are usually present in abundance; skeletal tissues and muscle are common.

Teratoid tumors are partly cystic and partly solid; the cysts are usually multiple, with one large cyst occupying the greater part of the tumor. Retroperitoneal teratoid tumors in infancy and childhood are not malignant in the strict pathologic sense, but they should be considered as malignant, in that they cause death; one-half of the tumors in the literature were described at autopsy. Later in life a malignant change may affect one or several of the constituent tissues, although not always in equal degree.

#### CLINICAL FEATURES

The ages of the 23 reported patients (Table 1) varied from new-born to 17 years. Eighteen of the children were below the age of 2 years. Both sexes were represented: 13 males, 8 females, and 2 not stated.

The history was that of enlargement of the abdomen, an abdominal mass usually being noted early in the course of the disease. The rate of growth of the tumor was not indicated in many of the reports, but some of the masses had not increased in size during observation for several months. Abdominal pain was an infrequent symptom; the early age of the patients was probably a factor. Later in the course of observation, fever, vomiting, loss of weight, anorexia, and constipation were occasionally noted. Although such tumors are in close proximity to the kidneys, urinary symptoms have not been observed.

On examination, an abdominal mass, firm in consistency, was noted in all cases. There was a striking difference in the location of the tumor; 13 masses occurred on the left side, 5 on the right side, and 5 on both sides of the abdomen. The large masses were usually found to extend beyond the midline to the opposite side, and were ballotable into the lumbar region. The size of the tumor was usually large in proportion to the child's abdomen, a frequent description being that of an adult head. Dilated veins of the abdominal wall were occasionally noted.

Röntgen studies were performed in only one case, revealing areas of ossification in the tumor. In this child, a pyelogram revealed a downward displacement of the kidney.

#### DIAGNOSIS

Retroperitoneal teratoid tumors in infancy and childhood may be differentiated from other tumors occurring in this region. As previously stated, neuroblastoma sympatheticeum is the most frequent retroperitoneal tumor in childhood. Symp-

TABLE 1

*Resumé of Cases of Retroperitoneal Tumors in Infancy and Childhood*

NO.	YEAR	REPORTED BY	AGE SEX	CLINICAL MANIFESTATIONS	SPECIMEN OBTAINED BY	TUMOR LOCATION SIZE CONSISTENCY GERM LAYER DERIVATIVES	OPERATION AND RESULT
1	1871	Dickinson (U. S. A.)	2 yrs. F.	Abdominal mass since age of 3 mos.; anorexia and fever (late)	Autopsy	Left half of abdomen 4 x 4 x 6 inches Cystic and solid Ectoderm and meso- derm	
2	1880	Hosmer (U. S. A.)	8 mos. F.	Abdominal en- largement since age of 1 mo.; anorexia, fever, and weight loss (late); abdomi- nal mass; di- lated veins of abdominal wall	Autopsy	Right half of abdomen Child's head Cystic and solid Ectoderm, entoderm, and mesoderm	
3	1898	Gude (Ger- many)	9 yrs. M.	Abdominal mass	Operation and au- topsy	L.L.Q. of abdomen 20 x 7 cm. Cystic and solid Ectoderm and meso- derm	Excision (partial) and marsupiali- zation (transperi- toneal) Death 9 days after operation
4	1904	Kou (Japan)	9 mos. M.	Abdominal mass	Operation	Left half of abdomen Child's head Ectoderm, entoderm, and mesoderm	Excision Death
5	1906	Schonholzer (Ger- many)	2 yrs. M.	Abdominal mass	Autopsy	L.U.Q. of abdomen 12 x 10 x 11 cm. Cystic and solid Ectoderm, entoderm, and mesoderm	
6	1907	Durante and David (France)	New born		Autopsy	Both sides of abdomen Fetal head Ectoderm and meso- derm	
7	1909	Jolinson and Lawrence (England)	3 yrs. M.	Abdominal mass for 3 mos.; sco- liosis of lumbar spine	Operation and au- topsy	Left half of abdomen 10 x 10 x 7.5 cm. Cystic and solid Ectoderm, entoderm, and mesoderm	Incision of cyst (ex- traperitoneal) Death
8	1909	Kolb (Ger- many)	7 wks. F.	Abdominal mass since age of 9 days; dilated veins of abdomi- nal wall	Autopsy	Left half of abdomen 12 x 15 x 7.5 cm. Cystic and solid Ectoderm, entoderm, and mesoderm	
9	1910	Kusnetzow (Ger- many)	4 mos. M.	Abdominal mass	Autopsy	7 mos. pregnant uterus Entoderm and meso- derm	
10	1911	Bauer (Ger- many)	14 yrs. M.	Abdominal en- largement for 5 mos.; abdomi- nal pain and loss of weight; ab- dominal mass; dilated veins of abdominal wall	Operation and au- topsy	Left half of abdomen Child's head Cystic and solid Ectoderm and meso- derm	Incision of cyst (ex- traperitoneal) Death 23 days after operation

TABLE 1—*Continued*

NO.	YEAR	REPORTED BY	AGE SEX	CLINICAL MANIFESTATIONS	SPECIMEN OBTAINED BY	TUMOR LOCATION SIZE CONSISTENCY GERM LAYER DERIVATIVES	OPERATION AND RESULT
11	1912	Sand and Lerat (Bel- gium)	15 yrs. M.	Abdominal mass for 10 yrs.; fever for 2 wks.	Operation	L.U.Q. of abdomen Large Cystic and solid Ectoderm, entoderm, and mesoderm	Exeision (extraperi- toneal) Death 9 wks. after operation
12	1919	Portugal (France)	17 yrs. F.	Abdominal mass for 9 yrs.; ab- dominal pain and vomiting for 8 yrs.	Operation and au- topsy	L.U.Q. of abdomen 12 x 7 cm. Cystic and solid Ectoderm and meso- derm	Ineision and marsu- pialization of eyst (transperitoneal) Death 4 days after operation
13	1920	Tsuda (Ja- pan)	17 mos. M.	Abdominal mass	Operation	Left half of abdomen Man's head Ectoderm, entoderm, and mesoderm	Excision Death 12 hrs. after operation
14	1924	Kaneko (Ja- pan)	10 mos. M.	Abdominal disten- sion since age of 4 mos.; abdomi- nal mass	Autopsy	Both sides of abdomen Man's head Ectoderm, entoderm, and mesoderm	
15	1926	Budde (Ger- many)	2 mos. M.	Abdominal en- largement and vomiting since age of 3 days; abdominal mass; dilated veins of abdominal wall	Operation and au- topsy	Both sides of abdomen Two fists Cystic and solid Ectoderm, entoderm, and mesoderm	Ineision (transperi- toneal) Death 4 days after operation
16	1927	Seki (Japan)	22 mos. M.	Abdominal mass	Autopsy	Left half of abdomen Infant's head Cystic and solid Ectoderm, entoderm, and mesoderm	
17	1931	Paltauf (Ger- many)	5 mos. F.	Abdominal mass	Autopsy	Left half of abdomen Fist Cystic and solid Ectoderm, entoderm, and mesoderm	
18	1932	Lightwood (England)	9 wks. F.	Abdominal en- largement and constipation since birth; ab- dominal mass X-ray: calcified areas; displace- ment of kidney downward in pyelogram	Operation	R.U.Q. of abdomen Orange Cystic and solid Ectoderm and meso- derm	Excision Recovery. No fol- low-up
19	1932	Probesse (Ger- many)	15 mos. F.	Abdominal mass since age of 3 mos.; loss of weight (late)	Autopsy	U.R.Q. of abdomen Ostrich egg Cystic and solid Ectoderm, entoderm, and mesoderm	
20	1932	Weier (Ger- many)	18 mos.	Abdominal en- largement for 5 mos.; abdomi- nal mass	Operation	Both sides of abdomen Large Cystic and solid Ectoderm, entoderm, and mesoderm	Excision (transperi- toneal) Recovery. Well 5 mos. after opera- tion

TABLE 1—*Concluded*

NO.	YEAR	REPORTED BY	AGE SEX	CLINICAL MANIFESTATIONS	SPECIMEN OBTAINED BY	TUMOR LOCATION SIZE CONSISTENCY GERM LAYER DERIVA- TIVES	OPERATION AND RESULT
21	1933	Watauabe (Japan)	23 mos.	Abdominal mass	Autopsy	Left side of abdomen 14 x 10.3 x 9.5 cm. Ectoderm and meso- derm	
22	1934	Terasako (Japan)	3 mos. M.	Abdominal mass	Autopsy	Right side of abdomen 15 x 9 x 8 cm. Ectoderm and meso- derm	
23	1938	Eerland (Holland)	8 mos. F.	Abdominal mass since age of 6 wks.	Operation	Both sides of abdomen Large Cystic and solid Ectoderm, endoderm, and mesoderm	Excision (extraperi- toneal) Recovery. Well 3 mos. after opera- tion

toms of weight loss, anorexia, and fatigue are more common in neuroblastomas, and the masses are usually nodular. Evidence of metastases to the liver or skeleton may be present. Plain roentgen films or pyelograms are of little aid in differentiating the two conditions, although areas of ossification would be suggestive of a teratoid tumor. Roentgen studies of the lungs or skeleton may reveal numerous small metastases of neuroblastomas.

The second most frequent retroperitoneal tumor in childhood is embryoma of the kidney. Urinary symptoms are rare in these cases, but hematuria is occasionally noted, and in such cases would indicate a tumor of renal origin. These tumors are smooth in outline, and are usually limited to one side of the abdomen. Pyelograms may show distortion of the renal pelvis, but may be normal, and do not give important differential information. In advanced cases of embryoma of the kidney, large fuzzy metastases may be noted on roentgen examination of the lungs.

#### TREATMENT

The treatment of retroperitoneal teratoid tumors is operative removal. The necessity for the removal of such tumors is evidenced by the deaths of the 12 untreated children. The operative mortality has been high, 8 of the 11 reported cases (72.7 per cent). The causes of death in the operative cases were incomplete removal, hemorrhage, and shock. The three operative recoveries were reported in the past decade, and these patients had the benefit of intravenous infusions and transfusions. A transperitoneal liberal incision is the best approach for the removal of these tumors.

#### SUMMARY

A case of retroperitoneal teratoid tumor in an infant 3 months of age, is reported. This is the fourth case in infancy and childhood in which the tumor has been successfully removed.

A review of the literature is presented.

I wish to acknowledge my indebtedness to Dr. Sadao Otani for the photographic preparations of the specimen.

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## THE SIGNIFICANCE OF SOMATIC STIGMATIZATION IN CHILDHOOD\*†

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When the clinician, accustomed to dealing with problems of disease, leaves the restricted area of his narrower field to venture into a more comprehensive neighboring area, he is accompanied by the secret fears of those he leaves, and is received by mistrust of those he approaches. He runs the double risk of losing something with the former group, and of not gaining much with the latter.

Some weeks ago I was invited by a group of psychiatrists in Boston interested in the problem of adoption, to discuss this problem from the genetic and eugenic point of view. In other words, I was asked: how far are we equipped to determine the biological value of a child in advance; are there any adequate methods available to determine this value before adoption? That leads us to the more general question: Are there any tangible, somatic signs present on the surface of a child which enable us to draw some conclusions about his inner value, and to come to a better understanding of his constitution which represents the sum of all his inherited chromosomal properties?

Pediatricians all too easily forget that life does not begin at birth, but nine months before—and just these nine months count more for our problem than does the entire subsequent life with all its environmental influences. That does not mean that I minimize the influence of environmental factors, such as disease, nutrition, climatic factors, psychologic and habit-forming influences, etc. I only wanted to restrict myself to the chromosomal and constitutional problem on this occasion, and within this problem to the significance of somatic stigmas in childhood.

Many of the stigmas and deviations from the norm are considered as mutations by some geneticists. In botany and zoölogy there are thousands of clear-cut examples illustrating the theory of mutations as a principle of evolution. It is a wrong concept to believe that something is lost when new mutations come into appearance. That is purely an anthropocentric idea. With regard to mutations, we are dealing with something new, but not always with a minus variation. That is the reason the term "degenerative type," for example, is misleading. Even if those stigmas and deviations from the norm often represent something pathologic, they still cannot be considered as proof against the theory of mutations as a principle of evolution.

Our specific problem of somatic stigmatization in childhood is only one of the few methods available to get an idea of the biological value of a child.

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There are six methods used in human genetics giving us some information on the biologic value of a child:

1. The normative investigation.
2. The hereditary statistics.
3. The study of the ancestors and siblings of the individual in question.
4. The pathology of identical twins.
5. The study of hereditary taints, i.e., inherited undesired properties of inferior value. Under this heading we will have to discuss the somatic stigmas in childhood.
6. The counterpart of No. 5: the study of talents, i.e., inherited properties of superior value.

Just as painstakingly as in any other science, the investigation of genetic problems has to distinguish between what can actually be observed from what can be only supposed, in order to explain more or less obscure phenomena. In any event, the fact is that the human being reveals innumerable characteristics based on "Anlagen" inherited from his ancestors. In this group belong, first of all, all those properties which characterize the human being as a member of the species "homo sapiens." Eugenics is not interested in that group of traits which all human beings possess in common. The eugenicist is more interested in those finer shades and differences which exist in human beings, particularly in the members of human society, in those belonging to a so-called "population." Those differences, dependent upon hereditary traits, are best designated as inherited properties of inferior value when they are undesirable, and as inherited properties of superior value when they are desirable. We are dealing, therefore, with a valuation which really presumes the establishment of a norm. From this conception of the norm, deviations toward properties of inferior value or toward properties of superior value have to be appraised.

Today I will discuss only Nos. 1 and 5, that is, the normative investigation and the study of hereditary taints.

As far as the first method, the conception of the norm, is concerned, I can be very brief. One may very easily become involved by making the statement that *this* is normal and *that* is a deviation from the norm. Hardly anything exists that can be called normal. There are only plus and minus variations, with a certain range, around the median values. Only the 100 per cent Darwinists have a simplified conception of the norm, which they consider to be the probability of preservation or the endangering of preservation. Those who look upon Darwinism not as a dogma but simply as a hypothesis will never arrive at the same deduction, but will look further for an empiric foundation. An individual *extremely well* adapted still cannot be considered as the goal of eugenics neither with regard to his physical nor to his mental habitus.

Empirically, a type constructed from the average values ascertained for each organ and each function in healthy human beings offers itself as the norm; but I am sorry to say, the establishment of this type is confronted with the greatest difficulties because of the great many transitional forms. The limit-values, according to the results of attempted measurements, have proved debatable

upon reexamination. I do not think that a "typical bodily constitution" can be derived from calculations of anthropometric data alone. The use of such indices in human genetics can be met only with scepticism. After all the misunderstandings to which the calculations of indices have led, with school children, e.g., the following will give you an idea of what was used for the construction of the norm: body weight, height, chest circumference, width of respiration, size of the heart, pulse rate and blood pressure.

Since 1922, when my interest was first stimulated in endocrinopathies, I have adopted the following program of studying *selected* clinical problems, which may have endocrinopathic or genopathic implications. It consists of the following partial components:

1. Exact and complete body measurements, compared with reliable modern standards, such as Meredith's standard. Evaluation of the proportions, particularly of the stem index and the skull index. In long periods of observation the velocity of growth and relative growth rate in per cent (Brodie's formula) must be included. The weight-height relation.

2. X-ray examination of the skeleton, particularly of the thorax and hands. According to Todd, the ossification and order of appearance of the growth centers is less important than the finer morphologic shades of the rest of the hand.

3. Sexual development, not so much the gonadal development in its narrower sense, but more the order of appearance of the extragenital characteristics, i.e., the question of harmonic or dysharmonic development. The quantitative side of the extragenital characteristics should also be considered. I have not yet included the determination of the sex hormones, but I believe that should be done. The basic values are still somewhat debatable.

4. Teeth and gums; here again x-ray examination of the jaws.

5. Examination of the heart.

6. Examination of the liver.

7. Study of somatic stigmas according to the following schedule:

*Mesenchymatous:* Marked brachycephalus (widening of the bridge of the nose); Dupuytren's contracture; contracture of the fifth finger; curved fifth finger; brachydactylia; arachnodactylia; congenital clubbed thumb; anomalies of the ribs; scaphoid scapula; cobbler breast; pigeon breast; malocclusion; arched palate; ear nodules; Darwin's tubercle; pitcher ears; hyperextensibility of the joints; knock-knees; cryptorchidism.

*Epithelial:* Adherent and missing earlobes; pseudo-Hutchinson teeth; epicanthus; hypermetropia; astigmatism; strabismus; accessory mamilla; pendulous breast; multiple nevi pigmentosi; dysharmonic development of secondary sex characteristics. Multiple stigmata and defects, difficult to classify.

Simple body measurements, including all indices whatsoever derived from them, are insufficient, as mentioned before; they are certainly valuable in constitutional pathology, but as far as their use in human genetics is concerned, I consider them to be just as inadequate as any other anthropometric procedure. First of all, one cannot accurately distinguish between that which is inherited and that which is the result of environmental influences by normative investiga-

tion, since it is expressed in one and the same figure. What Goethe, in the twilight of his life, said about meterology applies very well to anthropometrics: "It is a confused and intricate method." Its exactness is an apparent one. At the present time, it has no value for genetics. However, its value for constitutional pathology and anthropology is certainly not disparaged by this statement. An exact determination of the norm in the somatic sphere meets insurmountable difficulties, becoming even greater in the mental, intellectual, and psychic spheres; yet we know without measurements and figures what one must include under the heading of inferiority, average and superiority. The norm is an image which can be looked at, and appraised intuitively as well as by objective measurements, even though it does not always present itself to the external organs of sense.

It would be a mistake to underestimate the enormous amount of material which has accumulated in order to help clarify the ideal conception of the norm. When one attempts to apply it to an individual case, however, one may easily be misled. It is superfluous for the gross deviations, and insufficient for the finer shades.

The most important method in dealing with our particular problem is No. 5, the study of those hereditary taints, undesirable characteristics, which determine an individual as one of inferior value. What we are looking for are some definite somatic stigmas and deviations. It is obvious that attention was paid to the accumulation of prominent characteristics, in the somatic sphere particularly, and also in the psychic sphere. Some of them are designated as hereditary taints. It was thought that in this way keen insight might be gained into the mode of inheritance.

There are innumerable hereditary taints and stigmas which are striking because of their uniform significance, and of which the hereditary conditioning is painstakingly investigated; they can be overlooked by practical eugenics, however, because they are unessential or only rarely encountered. As geneticists and practical eugenicists, we have to distinguish between *manifest* and *latent* taints, and within each of these groups between the unessential, the essential but rare, the essential and frequent taints. So we come to six subdivisions.

*Manifest unessential taints* (about which one should know when discussing the biological value of an individual): Anomalies of refraction; ptosis of the eyelid; ophthalmoplegia; nystagmus; hernia; distichiasis (double rows of eyelashes); Dupuytren's contracture; epicanthus; missing fingers and some malformations of the fingers; lipomata; malocclusion, telangiectases; alopecia; appendages on the neck; coloboma; cryptorchidism; brachydaetylia; hemeralopia; anomalies of the nails; partial albinism; *pes valgus* (flat feet); Daltonism (color blindness); strabismus; amblyopia of one eye; web toes; cleft hand or cleft foot; syndactylia; cobbler and pigeon breast.

The above is a list of only the more frequent anomalies. There are many more. If only one or two are present in one individual, they are unessential and do not stigmatize the individual as one of inferior value. On the other hand, if they are accumulated in one and the same person, and particularly if

hereditary diseases have occurred in the family, then one has to be careful in his judgment of the biological value of the individual. In that case, these anomalies are an indication of a concealed or latent inferiority of the total personality. Mongolian idiocy, e.g., is one of the best examples of multiple anomalies with a definite anatomic lesion of the brain. In many cases of neurosis in children, as, for instance, cyclic vomiting, anorexia, obesity, essential leanness, migraine, I found an accumulation of all kinds of those stigmas in most of the cases. There are certain stigmas which occur together, such as brachycephalus and anomalies of the fingers. Here again, further progress is to be expected from the study of linkage in graded human characters.

In the pre-Mendelian period, those stigmas were overestimated. The classical geneticists no longer believe that there exists anything like a "degenerative type", revealing itself by stigmas. They only analyse the single (separate) anomalies which, independent of each other, are transmitted to the descendants. Only recently, more importance is being attributed to the fact that many hereditary taints occur in correlation to each other; and that latent peculiarities of the total personality are hidden behind some striking, but, in themselves, insignificant characteristics. Webbed toes, epicanthus, or partial albinism, for instance, are certainly unessential characteristics, but if, on the other hand, imbecility, epilepsy, or other mental inferiorities are found in the same family, then even those previously mentioned minor stigmas must be considered as having more serious significance.

At the present time we know more about the inheritance of prominent hereditary taints which occur only rarely, and which, therefore, are more striking than those which occur frequently, it is true, but which reveal themselves only in traces, predispositions or as starting points of morbid conditions. Here, too, the methods of unprejudiced theoretical investigation are not in agreement with those which eugenics has to follow in order to change and to eliminate the existing drawbacks.

Only a few words about the next groups since we find ourselves on shifting ground, about the manifest hereditary taints which are essential but rare. The principal difficulty lies in the uncertainty as to the manner in which these taints are transmitted. We do not even always know whether they are dominant or recessive, a fact which makes a great difference to the eugenicist. As long as we have no test for carriers of hereditary characters, so long will eugenics lack solid ground. To give you a practical example: Is a child coming from diabetic parents in danger of becoming a diabetic? Nobody can tell. On the whole, one is no longer confronted with purely scientific problems upon entering this field of eugenics. It is, to a certain extent, a matter of "*Weltanschauung*" and of personal taste as to how far one wants to go in drawing practical conclusions. The German law, for instance is entirely insufficient since it does not take the carriers into consideration. Eliminating only manifest cases may have its eugenic result perhaps after thousands of years.

The following is a brief list of hereditary traits which are considered essential but rare: microphthalmus; albinism of the eyes; amaurotic idiocy; aniridia

(absence of iris); total universal albinism; hemophilia; Huntington's chorea; glaucoma; hypospadias; hermaphroditism and pseudo-hermaphroditism; congenital malformations of the vagina and the uterus; myotonia; hemeralopia; otosclerosis; retinitis pigmentosa; Friedreich's ataxia; spastic spinal paralysis; atrophy of the optic nerve; deaf and dumbness; Parkinson's paralysis.

Practical conclusions: If one of the parents or siblings has one of these diseases or anomalies and the individual in question (probandus) shows one or the other somatic stigma, he has to be considered as one of inferior value. Adoption, for instance, had better not be considered.

The other subdivisions of hereditary taints cannot be discussed in relation to our problem, because of the paucity of exact material; even though just the latent traits one would consider the most important ones.

We have still to learn more about this branch of medicine. More and more data have to be collected. Pediatricians must become aware that they have more to do than to analyze and cure children's diseases. They have to learn to read and see the finer and apparently insignificant deviations from the norm on the *surface* of the child. I always remember with pleasure, when my teacher and old friend, Bela Schick, called our attention to some of the less known peculiarities of Mongolian idiocy, such as the missing tissue of the mammary gland at the time of birth or the deep insertion of the umbilicus.

There are other syndromes attracting the student's interest in somatic stigmatization, e.g., hypertelorism, dysostosis cleidocranialis, Laurence-Moon-Biedl syndrome, acrocephalosyndactylia and *symbrachycephalia*. Under this name there is comprised a big complex of anomalies of the hands, the arms and the thoracic wall. Numerous anomalies belong to the complete complex: syndactylia and brachydactylia, bowing of the arms, high placement of the scapula, scapulothoracic angle, defective development of the clavicle, asymmetry of the skeleton of the face, malformations of the sternum, scoliosis, partial or total absence of three to four ribs in the region of the pectoralis major muscle (first rib never involved). In addition to it changes of the skin and of the musculature. The pectoralis muscle and the intercostal muscles may be partially or totally absent. The nipple, too, may be absent or smaller than on the normal side; it may be higher placed and less pigmented. Also the web fingers and toes belong to this syndrome. Finally the inner viscera may be involved: herniation of the lungs, displacement of the heart and anomalies in the formation of the heart (patent foramen ovale, persistent ductus Botalli). In rare cases the spinal cord can be involved. Even if the complete picture is not seen in many instances there exists all transitional forms from one isolated stigma to the outspoken syndrome of *symbrachycephalia*.

I observed a peculiar syndrome in the Boston Floating Hospital some months ago:

A three months old female infant was referred because of failure to gain weight. Three sisters of the mother died during infancy, cause unknown.

Examination: Body weight 6 pounds, 3 ounces. Gain in weight always very slow. Constipation. The frontal region was somewhat more prominent.

(Caput piriforme). Anterior fontanelle wide open and displaced backward to the middle of the skull. Head circumference was 33 cm. Definite brachycephalus. Eyes were slanting downward. Distance between both eyes unusually wide and the bridge of the nose widened and flat. Both papillae were paler than usual. Hard palate was high arched. Malocclusion: Definite recession of the lower jaw. Left ear much longer than the right one with deformity. Darwin's tubercle present on the right ear. In the region of the coccygeal bone a small sinus was present. Skin over this region was covered with fine black hair. No spinal bifida by x-ray examination. Both lower abdominal quadrants were protruded, due to under-developed or missing external oblique abdominal muscles with herniation. Both knee joints seemed to be enlarged and the legs could not be completely extended. First toes on both feet were abnormally short, the second abnormally long, so that the feet resembled the feet of a monkey. X-ray examination of skull, spine and long bones showed no evidence of pathology. The baby seemed to be alert and smiled occasionally. Hearing and vision seemed to be impaired. The child took the formula slowly and regurgitated very often. The father had the same position of the eyes and also malocclusion.

This case belongs also to the syndrome of symbrachycephalia, a combination of mesenchymatous stigmata, involving the abdominal musculature, not the pectoralis muscle, so far not described.

This case shows: 1) the early diagnosis; 2) the fact that carriers of stigmata are sometimes of inferior value; this child, e.g., was a feeding problem from the start; 3) the significance of malocclusion; 4) heredity; 5) again the coincidence of anomalies of skull and extremities.

Another important problem is the study of the offspring of mothers with endocrinopathies and genopathies such as diabetes mellitus. I had this opportunity in Boston, working with Dr. Priscilla White. One child, e.g., almost three years old showed a severe malformation of his hands and feet; particularly the left foot looked quite mutilated and had no phalanges at all; there was syndactylia of the second and third metatarsals; the hands revealed complete development of the metacarpus but severe disturbances in the development of the phalanges with brachydaactylia of the thumb and malformation of the middle phalanx of the fifth finger. The differentiation of the wrist was somewhat delayed; the distal epiphysis of the radius was not yet present at thirteen months. In addition, the skeleton of the face was involved, showing an enormous widening of the bridge of the nose and an epicanthus on both eyes with strabismus. A sibling of the child, just recently born, did not show any signs of congenital anomalies except for a slight hydrocephalus. It seems to be very important to follow-up those babies born from diabetic mothers, very carefully, not only with regard to our knowledge of congenital malformations, but also from the eugenic point of view. Genetically it is all the same whether we investigate the diabetic patient himself or his offspring. Dr. White found about twenty-five per cent malformations in children born from diabetic mothers.

The diabetic child in general is a treasury for somatic stigmatization. It was the starting point in my studies of this problem. Since I came to this country,

my knowledge in this field has widened by the opportunity of following-up the large group of diabetic youngsters with the Joslin unit. On the whole I could confirm the experiences I had made in the old country. In addition to it I observed three cases which I consider important enough to be briefly discussed. We classified the cases under the heading "Multiple Stigmata and Defects". There was one boy and two girls. The boy showed, beside his stunted stature, marked brachydaetylia and was treated for hypothyroidism in another hospital. But the diagnosis was never quite certain. I rather believe that we are dealing with a primary genopathy and not with an endocrinopathy. One of the girls, belonging to the group of definite diabetic pseudo-dwarfism with hepatomegaly, showed brachycephalus, brachydaetylia and a rare peculiar lesion of the bones with a spontaneous fracture; the x-ray diagnosis was ambiguous between scurvy and aseptic (sterile) necrosis, similar to Koehler's, Schlatter-Osgood disease, etc. The second girl had a hereditary kyphoscoliosis (her father had the same anomaly) and a peculiar malformation of her hands. Previously she had been classified as a questionable case of achondroplasia, but we rather believe that she represents another congenital genopathy even if we cannot classify her under one of the common clinical headings. There exists, e.g., a congenital malformation described as acrocephalosyndactyilia which resembles an achondroplasia in some respects.

These three cases are transitional forms of the gross defects and malformations, such as diaphragmatic hernia, which we also found in one diabetic girl. They are certainly neither characteristic nor specific of diabetes mellitus and are seen as well in non-diabetic children. On the other hand, we can say they are more frequent in the non-diabetic child and are largely fortuitous if met with diabetes mellitus. The only definite fact we can establish from our investigation is that certain mesenchymatous stigmata seem to occur with a slightly higher incidence in the diabetic than in the non-diabetic child.

What do we learn from this fact and what conclusions can be drawn from it? If there is a deviation from the norm present somewhere in the chromosomal apparatus, which we have to consider as the carrier of the inherited predisposition and consequently of the constitution, usually it does not reveal the constitution as being abnormal as the only evidence, but it tends to coincide with more or less numerous other abnormal dispositions. Certainly these different deviations from the normal constitution are not at all of the same significance in their practical effect. While one group involves conditions of their carriers which are difficult to treat, the other stigmatizes him merely as being somewhat abnormal, and exert damage on him to far less an extent or not at all. This latter condition represents the so-called "state of degeneration" (*status degenerativus*), the combination of manifold inherited predispositions deviating from the norm and including the totality of the phenotype of the individual. Previously one erroneously characterized the manifold signs of an abnormal constitutional condition of the organism in the somatic and psychic sphere as "degenerative stigmatization". All these numerous carriers of the various accumulated constitutional deviations are the so-called "degeneratively stigmatized." It is a matter of

experience and quite intelligible that we so frequently meet genotypic diseases and variations among the victims of constitutional degeneration. There are all transitions from slight deviations to gross malformations which are seen also in individuals otherwise quite normal.

One more interesting detail may be emphasized. Quite frequently we find a combination of anomalies involving the skeleton of the face as well as the hands. We also know that from other multiple deviations in childhood, such as Mongolian idiocy, hypertelorism, acrocephalosyndactylia. We have met this combination for instance in the child of a diabetic mother, mentioned above. This coincidence of congenital anomalies may furnish a better knowledge of the linkage of the genes.

Has this investigation of congenital anomalies in the diabetic child and in the offspring of diabetic mothers also any practical interest? Very little can be said about it. But we have learned that in diabetics other gross lesions (besides the anomaly of the islands) are very seldom observed; only small insignificant stigmata are found. It looks as if a damage which has struck one of the vital organs has exploded and consumed its total energy. For other organs it works only as a glancing shot. Perhaps one can also reverse this statement and expect that those children of diabetic mothers with gross lesions will not develop diabetes in later life. Only the future will prove whether this hypothesis is right or wrong.

Coming to an end I readily admit that not everything presented in this paper was on solid ground. The subject I have discussed is still in a state of development. What I wanted to show was simply the way of proceeding in the analysis of somatic stigmatization in childhood to a certain extent, as a eugenic approach and not so much as a definite establishment of positive facts. This way of clinical observation may gradually change our outlook on diseases and so replace our analytical approach to pediatric problems by a more wholistic one.

## CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D. AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, November 13, 1940*

### Myeloblastic Leukemia with Confusing Leukosarcomatous Infiltrations Resembling Neoplasm

*[From the Medical Service of Dr. B. S. Oppenheimer]*

*History* (Adm. 461728; P.M. 11592). A man, aged 44 years, was admitted to the hospital on April 22, 1940 complaining of pain in the jaw and swollen glands in the neck. He was apparently in good health until three months before admission when he noted a painful, bluish spot on his gums in the region of the left lower molars. A dental diagnosis of an apical abscess was made and a molar was extracted. There was very little bleeding. The pain subsided only slightly and about three weeks later two more teeth were extracted for supposed abscesses. He then noted a small, firm gland in the left submaxillary area. Two weeks before admission, following the last tooth extraction, the lump in the left side of the neck increased rapidly in size and another small lump appeared in the left supraclavicular region. There was neither fever, anorexia, nor weight loss; he felt generally well.

*Examination.* The patient was a well developed, well nourished man who displayed obvious swelling of the left side of the neck. The sclerae were not icteric. Examination of the mouth showed the left lower posterior four teeth to be missing. The gum was covered with a pale grayish membrane, and was slightly tender. A firm, large, slightly tender, left submaxillary gland was felt and appeared to project into the floor of the mouth. A small left supraclavicular node, slightly movable, was also palpable. No other nodes were palpable. The heart and lungs were normal. The liver and spleen were not palpable.

*Laboratory data.* Blood: Hemoglobin, 106 per cent; white blood cells 7,000 with 82 per cent polymorphonuclear leucocytes, 8 per cent mononuclears, 8 per cent eosinophiles, and 2 per cent basophiles. Wassermann reaction negative. Urinalysis was normal. X-ray examination of the chest showed a faint clouding over the apex of the lung, probably due to thickening of the pleura.

*Course.* In view of the absence of fever and the discreteness of the node, it was felt that a neoplasm was the most likely diagnosis. A biopsy of the cervical node was performed and was reported as metastatic immature cell carcinoma. An aspiration biopsy of a node was reported as showing large, irregular cells suggestive of tumor cells; however, no definite diagnosis could be made on this material. The patient was treated with a course of intensive radiotherapy. The adenopathy subsided rapidly. He was discharged, to be observed in the radiotherapy department.

The patient was observed in the Out-Patient Radiotherapy Department where an extensive work-up was undertaken to determine the primary site of origin. Two chest plates were negative, a gastro-intestinal series was negative, x-ray examination of the mandible was negative. An x-ray examination of the paranasal sinus, however, showed clouding of the left antrum suggestive of a tumor in its floor. Accordingly, the patient was again admitted to the hospital for antrotomy.

*Second Admission:* (July 22, 1940). On examination he appeared to be chronically ill. There seemed to be some proliferation of tissue of the gums. A small, hard node was felt

below and behind the mandible. A firm liver edge was palpable two finger-breadths below the costal margin. A left crestedectomy was done, the antrum entered, and a normal mucosa was found with no mass present. Postoperative course was uneventful and he was discharged.

*Third admission.* (August 20, 1940). Dental x-ray films now seemed to indicate the presence of a sequestrum in the left mandible. The patient was admitted for a biopsy of the gum. This was reported as lymphosarcoma. He was discharged two days after admission.

*Fourth admission.* (August 27, 1940). Three weeks before this admission the submaxillary nodes returned, the patient became weaker, lost his appetite, and lost considerable weight. Profuse sweating, hoarseness and considerable difficulty in breathing developed. In addition, he developed episodes of pain and crampy stiffness in the left leg.

*Examination.* He appeared to have difficulty in breathing, and his face was somewhat swollen. The breath was foul. The voice was hoarse and rasping. The gum of the left lower jaw was indurated, swollen, and considerably ulcerated. The trachea was in the mid-line. There was marked enlargement of the submaxillary and submental nodes which were fused and encircled the anterior upper portion of the neck. Bean-sized, posterior cervical and axillary nodes were felt. Retromanubrial dullness was increased. The lungs appeared to be normal. The heart was normal. No abdominal viscera were palpable. Left ankle jerks and knee jerks were absent. Sensory status was intact.

*Laboratory data.* Blood: Hemoglobin, 88 per cent; white blood cells, 172,000 with 93 per cent blasts, 1 per cent myelocytes, 1 per cent metamyelocytes, 3 per cent polymorphonuclear leucocytes, 1 per cent eosinophiles, 1 per cent lymphocytes. Blood uric acid, 9.6 mg. per cent; urea nitrogen, 16 mg. per cent. Urine showed a faint trace of albumin.

*Course.* The patient ran a febrile course and on the sixth hospital day was found in coma. His respiration and pulse were normal. The pupils were unequal. The reflexes in lower extremities were absent. In the upper extremities the left reflexes were more active than the right. A lumbar puncture revealed faintly and uniformly blood tinged cerebrospinal fluid in all three tubes. He died on September 1, 1940, five months after the onset of his illness. It was felt that his death was due to a cerebral accident.

*Necropsy Findings.* The *spleen* was enlarged, weighing 600 grams. It was grayish in color, very cellular in appearance and had the disappearance of landmarks so characteristic of leukemia. The *liver* showed a very distinct exaggeration of the normal lobular structure; the periportal fields were infiltrated by leukemic cells. The *bone* marrow was very cellular and grayish, indicative of suppression of erythropoiesis. The *heart* on its surface had many gray nodules which infiltrated the myocardium; one such nodule infiltrated directly into the right auricle. The *kidneys* were so riddled with similar nodules as to strongly suggest the picture of a lymphosarcoma. These nodules were of a greenish hue (chloromatous). An incidental finding in the right kidney was a benign Grawitz tumor. The *adrenal* glands were surrounded by infiltrated periadrenal tissue. Similar tumor nodules were found all over the body, but were most numerous in the heart and kidneys.

*Comment.* *Dr. Klemperer.* The findings in the spleen, liver and bone marrow are quite compatible with the usual pathological picture of leukemia. However, the findings in other organs, especially the heart and kidneys indicate an aggressive, infiltrative morbid process such as lymphosarcomatosis. These findings testify to the close relationship that exists between leukemia and lymphosarcomatosis, and how difficult it may sometimes be to differentiate between the two without the aid of a blood count.

Reported by *Max Ellenberg, M.D.*

## THE STORY OF THE MOUNT SINAI HOSPITAL

*The Story of The Mount Sinai Hospital, of which the first eight installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninety-sixth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.\**

*The Jews' Hospital in New York was incorporated in 1852 by a group of public-spirited citizens, and in 1855 the doors of its first building on West Twenty-eighth Street were opened to receive patients. Staffed by some of the most prominent physicians of the day, the institution soon proved itself an excellent testing ground for the new methods and techniques which were being introduced into the rapidly broadening practice of medicine and surgery. During the Boyne Day riots, the cholera epidemic, and the Civil War, the Hospital showed its readiness to serve in time of crisis. In 1886 it was given its present name, The Mount Sinai Hospital. By this time it was out-growing its first home, and in 1872 moved to larger quarters at Lexington Avenue and Sixty-sixth Street, where the expansion in organization paralleled the growth in size and in medical resources. Here, during the next few years, the Out-Patient Department was formally established as an independent entity, the Medical Board was organized, the House Staff was enlarged, and the Medical and Surgical Services were separated for the first time. A number of new departments were organized, including New York's first Pediatric Service, under Dr. Abraham Jacobi, and in 1881 The Mount Sinai Training School for Nurses was established.*

### GROWTH AND DEVELOPMENT, 1870-1904

#### IX

The first ten years in the Lexington Avenue building were marked by great changes in the personnel of the Hospital Staff. Of those who had been its members in 1872, only three remained in 1882: the venerable Willard Parker, now eighty years old, and Thomas Markoe serving as Consulting Surgeons; and Abraham Jacobi still active as Attending Physician to the Children's Service. Three other members completed the Medical Staff of the Hospital. They were Alfred L. Loomis, an outstanding clinician and teacher,<sup>15</sup> who somewhat later, in 1855, was elected President of the New York Academy of Medicine; Henry N. Heineman, who was destined to become the Hospital's first Pathologist; and Julius Rudisch. The latter, while assisting Jacobi in his private practice, had been persuaded by him to become House Physician and Surgeon in 1875, the combined duties being still vested in one person.<sup>62</sup> When Dr. Jacobi, in 1879,

\* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete, are welcome and may be addressed to the Historian of the Hospital.

<sup>62</sup> Dr. Morris Manges' account of Julius Rudisch at Memorial Exercises for Dr. Rudisch, 1926.

became Pediatrician to the Hospital, Dr. Rudisch took over his duties as Attending Physician. At this time the special Department of Ophthalmology was headed by Dr. Gruening and in 1882, on the resignation of Dr. Noeggerath, Dr. Mundé became chief of the Gynecological Service.

During the same period there appeared on the Surgical Staff the names of four men who were to establish a great tradition for the Hospital. These were Daniel M. Stimson, William F. Fluhrer, John Allan Wyeth, and Arpad G. Gerster.



DANIEL M. STIMSON

Daniel Stimson, the son-in-law of Willard Parker,<sup>13</sup> and a follower of his school of surgery,<sup>15</sup> was above all a soldier. His portrait painted in the uniform of Surgeon to the Seventh Regiment shows a vigorous man of erect carriage and alert expression. His military bearing was characteristic of the manner in which he conducted his rounds. The House Surgeon was the only one he addressed at these times, and a too enthusiastic Junior who might break in with an eager explanation was silenced with a look, to be quietly rebuked after rounds were over. A cultured gentleman, a connoisseur of painting, his manner polished and courteous, Dr. Stimson was less formal after rounds. It was his invariable habit on arriving at the Hospital in his shining black barouche with its silver

lamps, to tip his own coachman a half-dollar—an act which caused considerable wonder on the part of observers. Dr. Stimson was a painstaking operator, but in cases that called for a procedure developed in pre-anesthetic days he showed an amazing rapidity that recalled the headlong speed of those earlier times.<sup>10</sup>



WILLIAM F. FLUHRER

William F. Fluhrer, a surgeon of the old school as far as aseptic methods were concerned, was a meticulous operator. Imperturbably calm, he would spend hours over an operation. If lunch time came, he would interrupt his work to consume a sandwich and a cup of coffee while the patient was carefully watched over by the anesthetist.<sup>10</sup> One such operation achieved the record time of eight hours.<sup>63</sup> On the other hand, this tall, dignified man whose manner seemed as

<sup>63</sup> Lilienthal, Howard: Looking Backward. The Medical Quip, January, 1924.

slow and quiet as his surgical technique, could show great speed in an emergency—as in his amputation of a leg in twenty seconds in a case of traumatic spreading gas gangrene.<sup>63</sup> Speed, indeed, was sometimes preferred to asepsis or antisepsis. The story is told by Dr. Lilienthal that Dr. Fluhrer, impatient with the lack of



JOHN ALLAN WYETH

progress being made by the younger surgeon during an operation, took the knife from his hand, sharpened it on his shoe, and proceeded to operate!<sup>10</sup> The patient recovered. Dr. Fluhrer was also ingenious in the designing of instruments and in the fashioning of wooden models for his inventions. He invented the alu-

minum probe for brain operations and a urethrotome which was prohibitive in price, but perfect in its function.<sup>63</sup> He was one of the few early American genito-urinary specialists.<sup>64</sup> In 1895 he was appointed head of the first such service established at Mount Sinai.

John Allan Wyeth, blue-eyed and suave, was a Southerner of quiet manner and iron determination, who became a pioneer in post-graduate medical teaching. At seventeen he was a soldier in the Confederate Army. Later he farmed to raise money for his education. After graduating from the University of Louisville he worked as a steamboat captain in order to earn enough for laboratory and post-graduate medical training. But on reaching New York in 1872, he found that no such thing as post-graduate medical schools existed. He took some courses at the Bellevue Medical College and as a demonstrator in anatomy, assisted Edward Gamaliel Janeway, the great diagnostician who himself was to join the Mount Sinai Staff in 1883. He then traveled abroad for two years, visiting various medical centers.<sup>65</sup> Returning to New York, he was appointed Attending Surgeon on the Mount Sinai Staff in 1882. The following year he realized his ambition to establish a school for medical graduates, the Polyclinic. On its first staff appeared the names of several Mount Sinai Attending: Dr. Wyeth and Dr. Gerster on the Surgical Service, Dr. Mundé on the Gynecological Service, and Dr. Gruening in the Eye Department.<sup>66</sup>

Dr. Wyeth's operating technique was characterized chiefly by the great calm and self-possession with which he worked. His operative clinics were extremely popular. The vivid descriptions of the procedure under way and the anatomy involved were delivered in so smooth a fashion that the student felt surgery might after all be as simple as Dr. Wyeth seemed to find it. Apparently nothing could disturb that monumental calm. One day when a particularly important patient on whom the surgeon had just finished operating was being carried from the room, the stretcher tipped and the middle-aged patient crashed to the floor. The only comment, made in that soft southern accent, was, "Isn't that too bad?" The patient recovered and was none the worse for the incident.<sup>10</sup>

With the appointment of Arpad G. Gerster to the Staff in 1880, the trend toward true aseptic and antiseptic surgery at Mount Sinai began. Born in Hungary in 1848, he was educated abroad and came under the influence of such great teachers as Rokitsansky, Skoda, and Billroth. He emigrated to the United States in 1873 and as he traveled across Europe he visited the various medical centers. Although "... surgical mortality was appalling" there were places, such as Volkmann's Clinic at Halle, where the newer Listerian methods seemed to be working miracles in reducing the death rate. Dr. Gerster landed in New York in 1874 at the time when "the towers of the Brooklyn Bridge stood as yet unconnected by cable. The water side was lined by a forest of masts, belonging mostly to square-rigged sailing vessels."<sup>15</sup>

<sup>63</sup> Interview with Dr. Charles Goodman, August 14, 1938.

<sup>64</sup> Address by Dr. D. Bryson Delavan at the unveiling of the statue of Dr. John Allan Wyeth at the Polyclinic Hospital on May 1, 1914 (in possession of the New York Academy of Medicine).

<sup>66</sup> Wyeth, John Allan: *With Sabre and Scalpel*. Harper & Bros., 1914.

Through a letter of introduction, Dr. Gerster met Ernst Krackowitzer, and after assisting him in operations at the German (now Lenox Hill) Hospital, of which Dr. Krackowitzer had been one of the founders, he became the older surgeon's assistant. Later he himself was appointed to the staff of the German Hospital.<sup>15</sup> Highly energetic, straightforward, equipped with a thorough med-



ARPAD G. GERSTER

ical education and a rich cultural background, Arpad Gerster was well fitted to be a leader. With Drs. Fred Lange of New York and Christian Fenger of Chicago, both of whom had also been educated in European medical schools, he was among the early advocates and chief exponents of aseptic procedure.<sup>67</sup> That he found the "...older men all attuned to pre-antiseptic methods"<sup>15</sup> is amply

<sup>67</sup> Mayo, William J.: *Early Days of the New York Surgical Society*. Cutting in possession of New York Academy of Medicine.

proved by such incidents as that of Dr. Fluhrer sharpening a knife on his shoe, or Dr. Neoggerath, in the days when women's hair was abundantly long, sewing up an incision with a hair extracted from the patient's head.<sup>68</sup>

In 1888, eight years after his appointment to the Mount Sinai Staff, Dr. Gerster published the first book on asepsis by an American author: *Rules of Aseptic and Antiseptic Surgery*. Previously works on the subject has been imported from England. It was also the first medical book to be illustrated with halftone plates, the photographs for which were taken by the author himself in the operating rooms of The Mount Sinai and German (Lenox Hill) Hospitals.<sup>69</sup> Just as Oliver Wendell Holmes in his treatise on puerperal fever forty-five years earlier had accused physicians of being carriers of disease, Dr. Gerster placed the responsibility for postoperative infection squarely on the shoulders of the surgeon.

"It cannot now be successfully denied," he wrote, "that the *surgeon's acts determine the fate of a fresh wound, and that its infection and suppuration are due to his technical faults of omission and commission.*" (The italics are Dr. Gerster's.)<sup>70</sup>

Concerning the fear of surgery which in the seventies and eighties characterized both patient and surgeon, he says: "The dread of undertaking and submitting to a surgical operation has greatly diminished, and timely, that is, early surgical interference has become more and more frequent, to the advantage of both patient and physician."<sup>70</sup> The declaration that, because of aseptic and antiseptic methods, "... surgery has become a *conservative* (the italics are again the author's) branch of the healing art"<sup>70</sup> was indeed the statement of one considerably in advance of his time.

In training the young men under him at the Hospital, Dr. Gerster insisted on the strict application of aseptic and antiseptic principles.<sup>71</sup> He was one of the first to break away from the older and cruder school of surgery, and to teach that human tissue is a delicate thing which must be delicately handled.<sup>72</sup> With his forceful personality, and blunt and direct approach, he was a teacher to be feared as well as liked and respected—"There was no fooling Gerster."<sup>73</sup> "The most brilliant operator and the most logical surgical thinker,"<sup>73</sup> his pupils found him a compelling instructor with a vast store of practical experience, information, and anecdote to share. A. A. Berg and Howard Lilienthal, both graduates of the Mount Sinai House Staff and eventually great surgeons in their own right and members of the Consulting Staff, were students of his teaching and assistants in his private practice. A versatile man with a great variety of interests, he was a musician, a painter, and in later years an etcher. A student of history and lover of literature, he was also an ardent fisherman and hunter, fond of taking long camping trips in the Adirondaeks, accompanied only by an Indian guide.<sup>73</sup> He

<sup>68</sup> Interview with Dr. Howard Lilienthal, April 5, 1939.

<sup>69</sup> Information from Appleton-Century Co.

<sup>70</sup> Gerster, Arpad G.: *Rules of Aseptic and Antiseptic Surgery*, D. Appleton & Co., 1888.

<sup>71</sup> Elsberg, Charles: Mount Sinai in the Late Nineties and the Beginning of Neurosurgery in the Hospital. *J. Mt. Sinai Hospital*, Vol. 4, No. 5, 1938.

<sup>72</sup> Interview with Dr. A. J. Rongy, April, 1939.

<sup>73</sup> Sachs, Bernard: Dr. Gerster as Man and Scholar. *Proceedings of the Charaka Club*, Vol. 6, Paul Hoeber, 1925.

was a man of practical bent and it was his delight to display to those who were interested the "German instrument pouch," a kit he carried strapped to the small of his back. This presented a somewhat terrifying aspect when, spreading the tails of his frock coat to sit down, he exposed to view the kit, "of ample proportions." It contained a collection of fine instruments, "... a supply of hardware which seemed enough for carrying out a major operative procedure."<sup>10</sup>

In the eighties and nineties patients were loath to go to a hospital and the more serious the case, the more anxious the patient's family to keep him at home. It was therefore quite customary for a surgeon to operate away from the hospital, often amid the filth and unsanitary conditions produced by the tenements. In his book Dr. Gerster devoted considerable space to the possibility of carrying out Listerian and aseptic surgery in a private home. The advice deserves quoting:

"A clean, well-lighted room is selected out of which all unnecessary furniture, hangings, etc., should be removed. A bare well-scrubbed floor is preferable to a carpet. One or two narrow kitchen tables, covered with a quilt and provided with a straw pillow, will make a capital operation table. A piece of rubber cloth (3 x 4 feet) is placed over the quilt, and a clean sheet is laid on the top. Fountain syringes are filled with a sublimate solution and placed on chairs to the right and left of the operating table, and suitably suspended from a nail or chandelier near the operating table. Two tin basins are filled with a corrosive sublimate solution and placed on chairs to the right and left of the operating table for the occasional rinsing of the hands of the operators and assistants. The author has found that it is very convenient to be independent of the patient's resources, as far as the necessary vessels for sponges and instruments are concerned. A nest of four good-sized block-tin wash basins, six tin soup basins (six inches in diameter) and four tin bake pans will serve every purpose and the small expense will be abundantly repaid by the cleanliness and sense of comfort that will result. The employment of copious irrigation during operations requires measures for protecting the person and clothing of the surgeon against the influence of the chemicals commonly used. An ample apron, made of light rubber sheeting and reaching from the chin to the toes is most convenient, and can be easily cleaned. The surgeon's shoes may be protected by a pair of light rubbers. However, they are apt to sweat the feet. The author overcame this drawback by the use, at the Hospital, of wooden pattens (French *sabots*) worn over the shoes. They are donned without the aid of the hands, and keep the feet warm and dry, and can be bought at 75 Essex Street, New York."<sup>70</sup>

The pre-Listerian methods of the older surgeons died hard and for some time the new surgery went on side by side with violations of its precepts. Nevertheless, the eighties saw the adoption at Mount Sinai of the sterilization of instruments in a solution of carbolic acid.<sup>10</sup> Major operations were infrequent. Despite the fact that Willard Parker had already performed the first appendectomy in the United States in 1864,<sup>74</sup> Dr. Gerster, as late as the eighties, was one of the

<sup>74</sup> Ruhrah, John: Willard Parker, Reprint Annals of Medical History, N. S. Vol. 5, Nos. 3, 4, 5.

few surgeons at the Hospital willing to operate on such cases.<sup>64</sup> By the middle eighties "... operations were done à la Lister under a cloud of carbolic acid vapor."<sup>13</sup> There was an attempt to arrange schedules so that the dirty cases followed clean ones, and "... after any particularly septic operation our operating room was sprayed for hours, or better still, all night with carbolic."<sup>13</sup>

*(To be continued)*

## William Branower

February 7, 1881–January 17, 1943

Dr. William Branower died January 17, 1943 at The Mount Sinai Hospital after a two year illness. He had given unsparingly and unstintingly of himself in his devotion to his professional duties to the very last day before the onset of his fatal illness. This outstanding feature of his character displayed itself at all times in many ways in his relationship to his family, friends and professional activities.

Born in Russia, Dr. Branower came to this country when a child. He attended City College and was graduated from the College of Physicians and Surgeons of Columbia University in 1904. Soon thereafter he became associated with The Mount Sinai Hospital, serving as an interne (1905–1906) and as Resident Surgeon in the Private Pavilion (1907–1908). He became anesthetist in 1908 serving at the same time as Assistant Surgeon in the Out-Patient Department. He became Chief of the Surgical Clinic and remained in that capacity for twelve years (1911–1923). He was Attending Anesthetist to the Hospital from 1923 to 1943.

A pioneer in the development of anesthesia as a specialty, Dr. Branower soon was an acknowledged and dominant leader in this rapidly developing field, so important to modern surgery. He was one of the original founders of the Committee on Fellowship of the American Society of Anesthetists and was a Diplomat of the American Board of Anesthesiology. In 1917 he was chosen President of the New York Society of Anesthetists. Throughout the years he contributed many scientific papers on Anesthesiology.

Dr. Branower was also a member of the American Society of Thoracic Surgery and the American Society of Regional Anesthesia.

The controlled Respirator devised by Dr. Branower and first demonstrated by him in 1935, is now in wide use in hospitals throughout the country.

In addition to his absorbing interest in his chosen field Dr. Branower engaged in many diversified activities, some closely related and others unrelated to his life work. For many years he had been an ardent student and later teacher of regional anesthesia. In the course of time he accumulated a splendid collection of anatomical models at a great cost. These he later used for teaching purposes and shortly before his last illness he donated the entire collection to The Mount Sinai Hospital.

As a member of the Board of Trustees of the Free Synagogue he had many opportunities, through manifold activities, to demonstrate his devotion to his fellow men.

Those who knew Branower well appreciated his sterling qualities which were displayed best at a social evening with his devoted family. His warm heartedness and his fine sense of humor delighted many and the earliest contact with him impressed one with the high cultural attainments of the man; Branower was, indeed, a scholar. He was respected by all and loved by those who knew him well.

J. L. MAYBAUM

## Max David Mayer

February 23, 1893—May 28, 1943

The life of man proceeds inexorably from the joyous miracle of birth to the shattering tragedy of the finale. Even in primitive times the tribesmen gathered at the side of the stricken comrade, and in their own way, and according to their understandings, sought to commend the soul of the departed to the gods. As one culture has succeeded another in human history these ceremonies have grown in complexity and pomp; have tended to become formalized and empty. It is therefore rather in the spirit of a simpler day when the leader of each family group was also its spiritual guide and adviser, that we have come here today to say "Hail and Farewell" to our dearly beloved friend.

United as we all are by the depth and intensity of our emotions, no words are needed to create the picture of Max David Mayer that each one of us will henceforth carry in his treasure chest of precious memories. Let me only remind you of his emotional intensity tempered by calm reason, his fierce devotion to duty illumined by his vivid sense of humor, his loyalties, his compassion, his tenderness, his selflessness, his uncompromising love of truth, and his deep sympathy with human vagaries. Let us never forget what he did for us, his friends. We would do well to honor his memory by striving to attain the same spirit of altruism.

Max David Mayer, the physician, may best be characterized in the words of the sage, Ben Sirach: "Honor a physician according to thy need of him with the honors due unto him; for verily the Lord hath created him. For from the Most High cometh healing; and from the King he shall receive a gift. The skill of the physician shall lift up his head; and in the sight of great men he shall be admired."

In the narrower sense of the word our friend was not a religious man, but we must recall that there is a faith expressed not in words, but in deeds. He may properly be looked upon as a veritable high-priest of life itself, presiding at its inception and following its tortuous path through joys and sorrows. A pioneer in the study of the relationships of mind and body, his mastery of both fields was unquestioned. He was the first man in the United States to establish a clinic where a woman's mind and a woman's body were considered in all their intricate interrelationships.

But the great field of medical endeavor could not claim all of Max's passionate interest. To art, literature and music he brought a rarely equalled sensitivity in appreciation and interpretation. His many friends among the artists, writers and musicians will bear testimony to his helpfulness in the solution of their technical problems, and to the stimulation and encouragement they owe to his teachings. We may truly marvel at the scope of his understanding, at the depth of his feeling and at the soundness of his critique.

The kindly hand of Time will gradually erase from our memory the sufferings that during this past year were bravely endured by our stout-hearted friend. Let us remember rather the great strong Max, serious, intent, arguing his points with cool logic; the tender, kindly Max, guiding a sufferer back to health; and the jolly happy Max, with eyes twinkling, telling a subtle tale or recounting a robustious story. This great human being, who has lived among us and worked with us all these years, leaves us now in a world that is far finer for his having passed through it. "The Lord hath given, and the Lord hath taken away. Blessed be the name of the Lord."

FREDERIC D. ZEMAN.\*

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Prolonged Survival after Perforation of the Infarcted Interventricular Septum in Coronary Arterial Disease.* S. E. MOOLTEN. Arch. Int. Med., 69: 108, January 1942.

Rupture of the left ventricle after infarction is immediately fatal unless the area of softening is situated in the interventricular septum. In the latter case death may be delayed several days, and then occur as a result primarily of the severe shock and heart failure resulting from coronary occlusion. Prolonged survival is rare and is characterized by intractable right ventricular failure and the presence of the harsh systolic murmur of interventricular septal defect.

The interventricular septum considered as a functional entity is of particular significance, both as a component of deep muscle tracts common to both ventricles and as an agency for protecting the right ventricle by preserving the differential in pressure between the two ventricles.

*Some Immediate Causes of Cardiac Infarction.* E. P. BOAS, Am. Heart J., 23: 1, January 1942.

The onset of cardiac infarction is often preceded by specific events that seem to be directly responsible. The most common external factors which precipitate cardiac infarction are effort, emotion, cold and over-eating. These factors do not cause cardiac infarction in the presence of normal coronary arteries. Coronary insufficiency arises because the narrowed channels of the diseased coronary arteries prevent the passage of enough blood to satisfy the needs of the heart muscle when called on for greater work; the flow of blood is decreased by reflex narrowing of the coronary arterial bed, or by hemorrhage into the coronary arterial wall, causing partial or complete occlusion of one of the coronary arteries.

*Alopecia from Cyverine Hydrochloride.* O. L. LEVIN AND H. T. BEHRMAN. J. A. M. A., 118: 41-43, January 1942.

In this paper the authors report the occurrence of alopecia following the use of a new antispasmodic drug. In this case, the defluvium followed the daily ingestion, for thirty days, of cyverine hydrochloride (Stearns) and rapidly progressed to involve the entire scalp.

A white woman aged 49 years ingested 920 mg. of cyverine hydrochloride, an antispasmodic drug, within a period of thirty days. At the end of this time alopecia of the scalp developed. The alopecia was progressive and resulted in approximately complete loss of hair from the scalp. The eyebrows and eyelashes turned a grayish white shortly after the occurrence of alopecia. There was an associated exfoliative dermatitis of the skin and a diminution in perspiration.

The suggestion is advanced that the effects of the drug on smooth muscle caused complete relaxation of the erector pili muscles around the hair follicles. In this manner loosening of the hair shaft and subsequent alopecia may have occurred.

*Technic of Tattooing with Mercury Sulfide for Pruritus Ani.* R. TURELL AND A. W. M. MARINO. *Ann. Surg.* 115: 126, January, 1942.

The authors briefly reviewed the history of therapeutic tattooing employed in surgery. The present therapeutic status of anal pruritus and the surgical anatomy of the anal canal were discussed. The technique of tattooing of the anal canal and the perianal region with mercury sulfide was detailed. The necessity of tattooing of the anal canal to the level of the pectinate line was stressed. The development of a simple, reciprocating, pneumatic tattooing pistol by the senior author was reported.

*Aplastic Anemia in Pregnancy.* E. S. HURWITT AND L. FIELD. *Am. J. Obst. & Gynec.* 43: 42, January 1942.

A case is presented of aplastic anemia occurring during pregnancy, with fatal issue; clinical, laboratory, and pathological data are given. Eighty cases of primary aplastic anemia in women were collected from the literature; 13 of these were found to be of obstetric significance. Of the total group of 14 cases of aplastic anemia during pregnancy, there were only 5 survivals. In all of these the uterus had been emptied, 2 by normal delivery at term and 2 by interruption during the third trimester. One case developed post partum. A fatality was recorded in each of the 3 cases in which there was no interruption of pregnancy. From the evidence at hand, it would appear probable that the occurrence of aplastic anemia during pregnancy may not be coincidental, but that the gravidity may play an etiologic or conditioning rôle. Interruption of pregnancy should be strongly considered in the presence of aplastic anemia.

*A Rapid Film Changer for Use in Contrast Angiocardiology.* M. L. SUSSMAN, M. F. STEINBERG, AND A. GRISHMAN. *Radiology* 38: 232-233, February 1942.

The following is a description of a simple, inexpensive apparatus designed for this purpose, with which eight roentgenograms of excellent quality can be produced. The apparatus consists of a wooden wheel 62 inches in diameter, mounted on an axle. Eight 10 × 12-inch cassettes are mounted radially. The wheel is turned by hand behind a lead screen in which there is a 10 × 12-inch opening. Each cassette passes behind this opening. An ordinary door stop serves to stop the wheel as each cassette arrives in position behind the opening in the lead screen. With practice, eight exposures can be made in ten seconds. It is easy to position the patient by preliminary fluoroscopy, one cassette being removed and replaced by a fluoroscopic screen held behind the opening in the lead screen.

*Ileocolostomy With Exclusion For Non-Specific Ileitis.* R. COLP, J. GARLOCK AND L. GINZBURG. *Am. J. Dig. Dis.* 9: 6468, February 1942.

In a series of 40 cases of regional ileitis treated by ileo-colostomy with exclusion no operative mortalities nor any serious postoperative complications were encountered. Two cases were complicated by large ileo-sigmoidal fistulae. In these cases, as anticipated, the operation was ineffective. There were three other cases which were unsuccessful. The remaining 35 cases showed recession of disease in the excluded loop. Proximal extension of the disease appears independent of the type of operation employed and occurred in one case. The authors stress the selection of a site which is sufficiently orad to avoid this complication.

Inspection of the translucency of the bowel is offered as a method for selecting such a site.

THE BÉLA SCHICK LECTURE<sup>1</sup>THE CHOICE OF TIME AND TYPE OF OPERATION IN SURGERY  
OF EARLY LIFE<sup>2</sup>WILLIAM E. LADD, M.D.<sup>3</sup>

[Boston, Mass.]

I feel greatly flattered at being selected by your committee to give the first of the Schick lectures.

It is indeed a great pleasure to come here to honor Dr. Béla Schick, one of the outstanding pioneers in Pediatrics. His research work on diphtheria, scarlet fever, tuberculosis and other disorders have brought him well deserved fame throughout the civilized world. Dr. Schick recognized soon after the turn of the century that the diseases of childhood were deserving of special study and, so far as I know, he has devoted his time to this branch of medicine ever since with the great success that is known to all.

Pediatrics has been established as a specialty for many years. Its justification as a specialty has been based on the fact that infants and children are subject to different disorders from the adult and react to the same ones in a different manner. It has often seemed strange to me that the surgeons have been so slow in recognizing that the same variants exist in the surgical maladies of early life. It is indeed still common for many surgeons to consider the infant as only a small sized adult and that he should be so treated.

This point of view, the failure to be familiar with the surgical conditions of early life and with the varied reactions that they manifest obviously leads to faulty diagnosis which in turn leads to poor treatment and results.

The surgeon who likewise fails to accustom himself to handling the delicate tissues of the infant and to the gentle use of small instruments and suture material can hardly hope to be successful in the management of the surgical problems of this age group.

The lack of appreciation of these factors often leads the surgeon, the general practitioner or even the pediatrician to advocate surgical procedures at disadvantageous times. Haste is not infrequently recommended when delay is more desirable, but perhaps more frequently delay is prescribed when prompt surgical intervention offers these young patients their best chance of recovery.

For example, it does not seem to be very common knowledge that infants in the first 48 hours of life stand major surgical procedures far better than they do a week or so later. It is also not uncommon practice for the same type of

<sup>1</sup> Lecture delivered in the Blumenthal Auditorium of The Mount Sinai Hospital, April 13, 1943.

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operation to be used on the child that is used in the adult when a modified or different technique is clearly indicated. Therefore, it seems not inappropriate to discuss the choice of time and type of operation in surgery of early life about which there is still a variance of opinion.

This lack of consensus is true with regard to the common conditions as well as to those that are less frequently observed.

There is perhaps no better example of a very common malady than that of inguinal hernia and perhaps none in which there is so great a variety of teachings and practices being carried out.

When an inguinal hernia has been diagnosed in a small infant, the question at once arises as to whether an operation should be done and, if so, what type of operation is best suited for this age group.

There are two forms of treatment for congenital inguinal hernia—the truss and the radical cure by operation. In infants the truss has a distinct field of usefulness although it is seldom or never curative. It is used as a temporary measure to hold up a hernia or to prevent strangulation or incarceration during periods of sickness or feeding difficulties of an infant during its first year of life. There are many forms of truss available, but the only one that has proved useful in our hands is the simple yarn truss. This is easily applied, is always available, is inexpensive and can be kept clean by daily washing. Most parents can be instructed in a few minutes about the details of its application, and can carry out the treatment successfully at home. However, there are instances in which the truss is ineffective due either to the size of the hernia or to the lack of aptitude of the parent. In such cases operation is resorted to regardless of age. The youngest patient I, personally, recall operating on for a strangulated hernia was a month old baby who had been born two months prematurely. The patient had an uncomplicated convalescence and a permanent cure. When operation is indicated, the choice of the type of operation is important as is the after care of the patient.

Broadly speaking, there are two types of operation for the radical cure of inguinal hernia—one in which the cord is transposed and the other in which the cord is returned to its normal position. The technique recommended by Bassini is perhaps the best known example of the first group, while that recommended by Ferguson is a good example of the second type. There are numerous minor variations of both these operations. In our opinion any operation transposing the cord should not be used in infants or young children, although such an operation is eminently satisfactory in older children or in adults. The reason for not transposing the cord in the younger patients is the danger of pressure on the delicate spermatic vessels with consequent interference with the blood supply and resulting atrophy of the testicle. The operation which has been eminently satisfactory at The Children's Hospital in over 3,000 cases consists in complete excision of the sac, tucking its stump under the abdominal wall, replacing the cord in its normal position, and suturing the external oblique, internal oblique and transversalis muscles together to Poupart's ligament and then overlapping the external oblique from below upwards. The English and Scotch surgeons

consider the complete excision of the sac as the most essential part of the operation and pay very little attention to the repair of the canal. While excision of the sac is unquestionably the most important part of the operation, it nevertheless seems logical to supplement this by an adequate repair of the canal, if it can be accomplished without interfering with the blood supply of the testicle.

One reason why some surgeons still advocate postponing the operation for the cure of inguinal hernia until the child is seven or eight years old is their fear of sepsis in the wound from soiling with urine. This can easily be avoided by the simple care devised by Sir Harold Stiles many years ago. This consists in applying a small collodian dressing to the wound and then when the child is placed in the crib his four extremities are tied to the four corners of the crib sufficiently tightly to prevent him from pulling off the dressing or turning over, but loosely enough to allow considerable motion. A fracture cradle is placed over the infant and one end of a diaper is placed under his buttocks and the other end is pinned to the top of the fracture cradle. A diaper so placed catches all urine voided from an infant of either sex and keeps the dressing completely dry. If the above principles are adhered to, infants of almost any age may be operated on successfully with a negligible mortality, recurrence or testicular atrophy. However, if the use of the yarn truss proves effective and is well tolerated by the parent and the child, the operation can be more easily done after the first year and should be delayed longer than that time by the surgeon who operates only occasionally on infants.

The teachings and practices in caring for patients with umbilical hernia have also many variations. In this condition there is no problem of diagnosis, but there is the problem of knowing how large an umbilical hernia can be cured by strapping, how long this treatment should be persisted in, and what type of operation should be done when it has been decided that surgery is indicated. The vast majority of infants in their first year of life that come to our clinic for the relief of umbilical hernia are never operated on for this condition. These are the infants whose umbilical ring will admit the tip of the little finger and whose sac protrudes a half to an inch above the level of the abdominal wall. Hernias of this size can almost always be cured by strapping with adhesive. The tongue and slot strapping has proved most effective and is the easiest type of strapping for a parent to apply successfully at home. The common practice of inserting a coin or a button into the ring is illogical. It is like putting one's foot in the jam of a door and trying to close the door. Umbilical herniae larger than that described or those in which strapping has proved ineffectual require operation.

An operation for umbilical hernia which excises the umbilicus in a child may cause considerable mental anguish, so for that reason it is desirable to preserve the umbilicus. A U-shaped incision is made with the bottom of the "U" below the umbilicus. This flap of skin and subcutaneous tissue are raised freeing the skin of the umbilicus from the underlying peritoneal sac. The sac is next excised and the peritoneum closed. The rectus fascia is undermined and overlapped with a row of mattress sutures of silk and a second row of interrupted sutures to the free edge.

The larger defects of the umbilicus which are seen at birth and which are caused by an arrest in development at an earlier stage of embryonic life present a much more difficult problem. These herniae commonly called omphalocele are covered only by the membranes of the cord in some cases and in other instances they are partly covered by skin and partly by membranes.

Such patients should be treated as surgical emergencies and should be operated upon as soon after birth as possible for two reasons. First, on account of the danger of rupture of the membranes and consequent exposure of the abdominal viscera to infection; second, because infants in the first 48 hours of life tolerate major surgical procedures far better than a few days later. Early operation is particularly important in this situation on account of the possibility of not being able to replace the abdominal viscera within the abdominal cavity due to intestinal distention or obstruction.

Even in the patients seen directly after birth the problem of placing the viscera within an abdomen that has never been developed to hold them may prove difficult. A few hours spent in preparation with gastric suction, a rectal tube, and a tent with high concentration of oxygen may make the difference of being able or of not being able to return the viscera to the abdominal cavity. The two-stage operation is a life-saving procedure in cases in which the viscera cannot be returned to the abdomen or in cases in which the tension is too great for an adequate repair of the abdominal wall. In the first stage, the skin and subcutaneous tissues are undercut and freed so that they can be sewed over the viscera. At the second stage, five or six days later, this wound is taken down and it will be found at this time that the abdominal musculature will have become sufficiently stretched to allow a good and permanent repair.

Until very recent years congenital diaphragmatic hernia has been a baffling problem. In 1931 Hedblom made a very extensive review of the literature which showed that 75 per cent of patients with congenital diaphragmatic hernia died in the first month of life and if this observation had excluded the herniae through the esophageal hiatus the mortality would have been nearer 90 percent. As recently as 1936 Orr could find but 9 patients who had survived operation in the first year of life. In the older records of the Children's Hospital 9 patients with diaphragmatic hernia were treated by the non-operative or waiting policy. Of these only one is known to have survived and that one had a hernia through the esophageal hiatus.

The four situations in the diaphragm where hernia may take place are the right and left pleuro-peritoneal canal (the foramen of Bochdalek), the substernal opening known as the foramen of Morgagni, and the esophageal hiatus. Of these openings by far the commonest and the one that causes by far the most serious difficulty is the foramen of Bochdalek.

Herniae involving this opening often have no sac and allow practically all the abdominal organs to go into the thorax. Here, as one would expect, they may cause respiratory, circulatory or digestive symptoms. If the obstetricians and pediatricians will remember that diaphragmatic hernia is one of the causes of cyanosis, circulatory collapse or vomiting in the newborn and send the patient

promptly for surgical intervention, many lives will be saved which otherwise would be lost.

With our recent advances in the surgical treatment and the futility of expectant measures, there can be no argument but that early operation is the best treatment for most congenital diaphragmatic hernia. The optimum time for surgical intervention is in the first 48 hours of life before the intestine has become distended. It is our belief that there are many cases of diaphragmatic hernia in infants in which it would be impossible to reduce the hernia through a thoracic approach. We therefore use the abdominal route.

A few hours spent in preparing the patient for operation may make a great difference in the ease with which the operation can be performed and even may make a difference of a fatal or successful outcome. The small patient is given vitamin K or a small transfusion to counteract any bleeding tendency. The infant is then placed on gastric suction, has a rectal tube inserted, and then is placed in an oxygen tent with high concentration of oxygen in order to reduce to a minimum the amount of distention of the intestine.

TABLE I  
*Total number of cases operated upon 29*

SITE OF HERNIA	NUMBER
Left Bochdalek.....	20
Right Bochdalek.....	4
Esophageal Hiatus.....	2
Foramen of Morgagni.....	3

Cyclopropane is a particularly appropriate anesthetic for these cases on account of its high content of oxygen. Its disadvantage is, of course, its inflammability.

In herniae through the pleuro-peritoneal canals, a rectus muscle splitting incision can be used. In cases where the defect is in the foramen of Morgagni or the esophageal hiatus, a paramedian incision is satisfactory. The herniae through the esophageal hiatus are the only ones in which there can be any argument about the merits of an abdominal or thoracic approach. In these instances either approach can be used but even here we prefer the abdominal approach.

The question of the desirability of crushing the phrenic nerve is worthy of consideration. As a palliative procedure, it is valueless and dangerous. When it is done as the first step of the operation for the repair of the diaphragm it has some merit. It allows the diaphragm to be handled a little more easily and theoretically it allows for better healing. In our more recent cases we have not crushed the phrenic nerve and the diaphragm has healed well. It is our present feeling that the advantages of this extra step are not worth the extra time it requires.

In the herniations through the foramen of Bochdalek in which there is no sac most of the abdominal viscera are above the diaphragm. These are first reduced

below the diaphragm and then wrapped in warm moist gauze outside the abdomen. The edges of the defect in the diaphragm are next denuded and the opening is closed with one row of mattress sutures of silk and a row of interrupted sutures of the same material. The abdominal viscera are then returned to their proper position when possible and the abdominal incision is closed in layers. In a few instances this is not possible or if done the viscera are so compressed that they cannot function. Under such circumstances a two-stage closure of the abdominal wound, as has been described above in the repair of an omphalocele, has proved to be a life-saving procedure.

By following these policies in selecting our time and type of operation, we have dropped the mortality of congenital diaphragmatic hernia by 70 odd per cent.

The indication for operation in cases of malrotation of the intestine are not dictated by the age of the patient, but rather by the appearance and the severity of symptoms. Symptoms may arise soon after birth and be those of almost complete obstruction, in which case an immediate operation is indicated, or those same symptoms may appear later in life and operation of course is undertaken only when the obstructive symptoms occur. In other instances, faults of rotation may cause less definite symptoms such as vague intermittent pain, inter-

TABLE II  
*Cases of diaphragmatic hernia at The Children's Hospital*

Total series (3 cases cannot be traced).....	39	
Number of cases unoperated.....	7 (6 deaths)	85.7%
Number of cases operated upon.....	29 (8 deaths)	27.5%
Number of cases operated upon since 1940.....	10 (1 death)	10.0%

ference with digestion and failure to gain weight. In such cases operative interference is only resorted to after expectant or medical measures have failed. It should be emphasized that incomplete rotation of the bowel is not in itself an indication for surgical interference and that presumably there are individuals who go through life with this condition without experiencing any symptoms or interference with health.

When, however, surgical interference is indicated, the type of operation resorted to is of paramount importance as we have learned from bitter experience. In the cases in which midgut volvulus has taken place and the obstruction is almost complete, the first step is to deliver the whole midgut outside the abdominal wall. It is impossible to define accurately the existing pathology without doing this. After doing this one can see whether the volvulus has taken place in the usual clockwise direction or in the unusual counter-clockwise direction. The volvulus is next untwisted, the congestion of the bowel is quickly relieved and its color returns to normal. At this point the surgeon is prone to conclude that the obstruction has been relieved and that the patient will be cured. Such a conclusion has been one hundred per cent erroneous in our experience. The next step in the operation should be to expose the duodenum throughout its whole length, and invariably one will find some congenital bands which if not

severed will cause return of the symptoms and a probable fatal outcome. The bowel is then returned to the abdominal cavity leaving the cecum in the left upper quadrant. We have made no attempt to restore normal anatomic relations for several reasons. It would be a long and difficult operation to accurately attach the mesentery of the small bowel, the cecum, the ascending colon, and the hepatic flexure in their normal anatomical positions. If this were done inaccurately, the superior mesenteric artery might be drawn too tightly across the duodenum causing a return of the obstruction or if a hiatus were left an ideal situation would exist for a concealed hernia to develop. Perhaps the best reason of all for not attempting this restoration is that the bowel functions perfectly in its abnormal position, providing the other steps in the operation have been properly performed.

In cases of obstruction due to malrotation without volvulus the exposure of the whole duodenum and severing of all congenital bands constricting its lumen has proved quite satisfactory.

TABLE III

*Results of operative treatment in 59 cases of congenital extrinsic intestinal obstruction*

OPERATION	DEATHS	RECOVERIES
Reduction of volvulus.....	6	0
Anterior gastric enterostomy.....	1	0
Miscellaneous procedures.....	5	0
Ladd's operation.....	10	37
Totals.....	22	37

Congenital atresia of the alimentary tract may take place at any level from the esophagus to the anus and all require operation at the earliest possible time. In the stenoses cases when the obstruction is almost complete, the same rule holds good but there is an occasional case in which the narrowing is less marked and in which the urgency of relief is less great. Until recently we considered that the danger of perforation or gangrene in a case of atresia was not great in the first week of life. In the last few months, however, we have seen cases in which gangrene, perforation or both have taken place within the first 48 hours of life which makes the urgency of operation even greater.

In patients with imperforate rectum and anus the choice of operation depends on the type of the malformation. The variations in the malforma can be accurately demonstrated by the x-ray examination without the use of contrast media. By taking a plate with the patient in the inverted position the site of the blind end of the rectum can be demonstrated by the air in it. The distance between the blind end of the rectum and the anus dictate whether the surgical approach should be abdominal or perineal. Roughly speaking, it is unwise to attempt to bring the rectum down by the perineal approach when it is much over 2 centimeters from the anus. In the early days of our work in this field most of

our failures were due to adopting the perineal approach in cases in which the rectum was too far away. This resulted in a long unsuccessful search for the rectum below which had to be supplemented by a laparotomy and a colostomy at the same time. When in doubt as to the best approach, it is best to do a laparotomy and a simple colostomy at the first operation. The colostomy should be placed high enough in the descending colon so that it will not hold up the rectum when that is brought down at a later time. At the second operation, some weeks or months later, considerable help can be obtained in identifying the rectal pouch by passing a large sized rubber catheter to its bottom through the colostomy opening. It is also helpful to have a catheter in the urethra so that it can be more easily seen and not injured. The perineal approach to the rectum has usually been made by a median incision, starting in front of the anus and carried back to the coccyx. The ischiorectal fossa is entered and the rectum freed until it can be brought to the anus without tension. It is then opened and stitched to the anus and the remainder of the perineal incision closed in front and behind it. If the rectal pouch has been adequately freed so that it can be stitched to the anus without tension one may expect good healing and a good result. If, however, it is impossible to avoid tension one is likely to have a stricture formation at the anus which requires a long period of dilatations.

As with imperforate anus, a fairly accurate diagnosis of atresia of the small bowel may be made by x-ray examination without the use of contrast media. Atresia of the small bowel should be operated on as early as possible. A primary anastomosis is the operation of choice. This anastomosis must be of the lateral type on account of the discrepancy in size between the proximal and distal segments of the bowel. The extremely small size of the distal segment presents technical difficulties which can be partially overcome by dilating it with a small catheter and salt solution or with a needle and syringe as recommended by Wangenstein.

If the atresia is in the duodenum, some additional problems arise. The operation of choice is a retro-colic duodeno-jejunostomy. In some instances this is technically very difficult and a duodeno-jejunostomy in front of the colon or a posterior gastro-jejunostomy may have to be substituted. In case the latter operation is substituted, it may have to be supplemented later by a duodeno-jejunostomy to prevent the reflux of the biliary and pancreatic juices into the stomach. It is very difficult, except at post-mortem examination, to differentiate between stenosis and atresia of the duodenum so in evaluating our results of treatment of obstruction at this level, we consider the two groups as one.

Until very recently atresia of the esophagus has carried with it a 100 per cent mortality. It is only by the study of our failures and the pathologic material that we begin to see the light. The two main causes of death in these patients are starvation and aspiration pneumonia. Of these two factors, the pneumonia is the more difficult to eliminate.

The type of operation offering the best hope of success depends on the type of malformation. This can be quite accurately determined by x-ray examination. One can place these malformations into five groups. First, those in which

both segments of the esophagus end blindly neither connecting with the trachea; second, in which the lower segment of the esophagus ends blindly and the upper segment is connected to the trachea by a fistulous tract; third, in which the upper segment ends blindly and the lower is connected to the trachea above its bifurcation by a fistula; fourth, in which the condition is much like the third except that the lower segment enters the trachea at the carina; and fifth, in which both ends are connected to the trachea by fistulae. In these broad groups there are many minor variations. The groups in which the upper end of the esophagus ends blindly and the lower end is connected to the esophagus by a fistula is by far the commonest.

The operations which have been attempted for the relief of this condition are gastrostomy, end-to-end anastomosis, marsupialization of the ends of the esophagus in the back. Gastrostomy alone is an almost valueless procedure, as in the patients with a tracheo-esophageal fistula of the lower segment the food which is given by gastrostomy goes back into the lung and the patients soon dies

TABLE IV

*Operative results in 87 cases with intrinsic obstruction (atresia or stenosis) of the intestine or colon*

SITE OF ATRESIA OR STENOSIS	NUMBER OF CASES TREATED	RESULTS	
		Deaths	Recoveries
Duodenum.....	21	10	11
Jejunum.....	8	4	4
Ileum.....	47	39	8
Ileo-cecal valve.....	4	4	0
Colon.....	4	3	1
Multiple lesions.....	3	3	0
Totals.....	87	63	23

of aspiration pneumonia. Even in the cases in which the lower end of the esophagus does not connect with the trachea the saliva enters the lung either by the upper fistula, if present, or if such is not present by collecting in the pharynx and being aspirated. In either case the same fatal result may be expected. An end-to-end anastomosis if it could be successful would be the operation of choice. The technical difficulties are great on account of the structure of the esophagus and on account of the fact that the two ends of the esophagus are apt to be far apart. In an examination of our pathologic material there were only 7 cases out of 43 in which the distance between the two ends were noted to be less than one centimeter. The distance in the other cases in which it was noted varied from 1 cm. up to 5.5 cm. It is difficult to mobilize the esophagus and if the two ends cannot be brought together without tension a leak and fatal mediastinitis is almost certain to develop. With these facts in mind, I have recently concentrated on trying to combat the two main causes of death in the safest way and as the result of this latest effort we have 4 surviving patients.

The first or oldest patient belonged to the group having the upper segment of the esophagus ending blindly and the lower segment connected to the trachea by a fistula. This patient had had a gastrostomy performed in another hospital and came to our clinic in a precarious condition from her pneumonia. The first step consisted in tying off the tracheo-esophageal fistula by an extra-pleural approach through the right back. The second step consisted in delivering the upper segment of the esophagus into the neck to allow the saliva to drain over the chest wall. The result of these two operations allowed the patient to recover from her pneumonia and to be fed without danger of recurrence from aspiration of food or saliva. Next an anterior thoracic esophagus was made by multiple plastic procedures. This new esophagus is functioning moderately well and the child now over  $3\frac{1}{2}$  years of age is in good health.

Our second living case belongs to the group having both ends of the esophagus ending blindly. In this case a gastrostomy has been performed and the upper segment of the esophagus brought out into the neck. Later when the child was a little over a year old the lower end of the segment of the esophagus was brought down through the diaphragm and out onto the chest wall to replace the gastrostomy by which the child had been fed up to this time. A skin tube was now made joining the upper and lower segments of the esophagus on the anterior chest wall. This child has also done well, has gained weight, and is in good condition except for a small fistula in the lower end of the skin tube. This is expected to close spontaneously. The two other young patients, who are now 6 and 5 months respectively, bid fair to do well. The youngest one, however, has recently had a severe nutritional break from which he is now recovering.

It is my firm conviction that too little attention has been paid to the surgical problems of early life and that many advances may be made in the future by concentrated effort in this field.

# A CASE OF NEUROFIBROMATOSIS IN A CHILD 5 $\frac{3}{4}$ YEARS OF AGE<sup>1</sup>

BÉLA SCHICK, M.D.

## CASE REPORT

*History* (Adm. 488777). L. G. was seen by me for the first time in May, 1937, when she was 5 $\frac{3}{4}$  years old. I was told that during July 1934 she had swallowed a metallic bead and soon afterward started to cough. The cough was slightly productive and lasted two months. A tuberculin test at that time was reported as negative. She was fluoroscoped by the family physician who discovered no foreign body but an extensive mediastinal shadow on the right side. The child coughed during the summer seasons of 1934 and 1935, but was otherwise symptom-free. A pediatrician saw the child in 1935 and considered the shadow to be that of a gland. Two months before admission to The Mount Sinai Hospital the child was again fluoroscoped by her family physician who found that the shadow had increased in size. The patient was seen by Dr. Ornstein who referred her to me.

The child was well developed, well nourished, of healthy appearance with no respiratory difficulty or cyanosis. Over the right upper portion of the chest anteriorly extending to the right shoulder and right upper arm superficial veins were prominent and dilated. Small shotty cervical axillary and inguinal nodes were palpable. The trachea was deviated to the left. Over the right upper chest anteriorly there was a slight impairment of resonance extending from the clavicle down to the third intercostal space. The breath sounds were slightly suppressed anteriorly and posteriorly, otherwise the examination was negative. The blood pressure was 120 systolic and 76 diastolic in both arms. Hemoglobin, 86 per cent; white blood cells, 14,500 with 68 per cent polymorphonuclear leucocytes. Laryngeal examination was negative.

X-ray examination of the chest showed a huge lobulated shadow occupying the upper two-thirds of the right chest in its mediastinal aspect, situated posteriorly (fig. 1). In addition to the two main lobulations there was an extension of the shadow paravertebrally down to the diaphragm. The trachea deviated to the left. The lungs were negative. Slight scoliosis was noted. As mentioned, this tumor mass had become larger when compared with the film taken three years previously. All bones were negative. The complexion of the skin showed a dark hue. There were numerous brownish-yellow pigmented areas 1 to 6 to 7 cm. in diameter scattered over the entire body. Tuberculin tests were negative. Temperature was normal.

The child was admitted to the Pediatric Service of The Mount Sinai for exploratory thoracotomy or x-ray treatment because of the increasing size of the mass and deviation of the trachea.

*Course:* The slow growth of the tumor together with the child's excellent general condition pointed away from malignancy. The diagnosis made was a dermoid tumor or neurofibroma. Dr. Neuhof's Surgical Service was called into consultation and expressed the view that exploratory thoracotomy was indicated because of the pronounced dislocation of the trachea, neck and chest.

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<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

Exploratory mediastinotomy and thoracotomy were performed through a right-sided paravertebral incision. After incision of the erector-spinae muscles there was escape of a small gelatinous looking mass, which was part of the tumor. Exploration revealed, furthermore, a large lobulated solid tumor, which was too fixed for safe removal. Small finger-like projections were removed for microscopic examination. The pathologic specimen was reported by Dr. Otani to be Neurofibroma.

The patient made an uneventful recovery. Radiotherapy of the chest was instituted and the patient was discharged with the advice to continue this treatment. For two years there was no particular change in the condition of the child. In March 1939 the mother noted an increase in the number and size of brown macular pigmented areas over the skin.



FIG. 1. Neurofibroma of posterior mediastinum. The sharply demarcated lobulated mass adjacent to the mediastinum was seen to be situated posterior on the lateral view. The posterior portions of the upper five ribs on the right side are narrowed as a result of the pressure of the growth.

The child was observed through 1940 and 1941. Her condition was satisfactory. The tumor in the mediastinum grew only in keeping with the growth of the body.

On April 7, 1942 a node was palpable on the right side of the neck. The patient was readmitted on April 23, 1942 because the node was growing. Numerous café-au-lait macular areas were present over the trunk. There was a small mass situated in the sixth interspace on the right side in the mid-clavicular line. The patient showed a distinct Horner syndrome on the right side. On the right sterno-mastoid muscle posterior to the midportion was an egg-shaped smooth fixed mass. At the operation it emerged from the intervertebral foramen and was adherent to a cervical nerve. The tumor could be dissected from the nerve, which was infiltrated with neoplastic tissue. The postoperative course was uneventful. The histologic examination by Dr. Otani again showed neurofibroma. When last seen in May 1943, the general condition of the child was entirely satisfactory and there were no new neurofibromata.

## COMMENT

Neurofibromatosis of von Recklinghausen is a disease characterized by tumors of peripheral nerves producing nodules in the subcutaneous tissue and in the skin. It is a generalized disease involving nervous tissue in any part of the organism. Therefore, the picture of the disease may be very bizarre. The tumors, frequently multiple, arise from the sheaths of the spinal and cranial nerves and produce symptoms by pressure on neighboring organs. Ewing states that the intestinal tract, bladder, pleural cavity, suprarenal gland, and terminal filaments of the sympathetic nervous system may be involved.

The second characteristic of the disease is the presence of areas of yellow or brown pigmentation scattered over the skin. These areas are of varying size, irregular in shape, sometimes when small resembling freckles. The whole skin may be rather dark. There may exist numerous cutaneous tumors of different size from tiny papules (1-2 mm.) to tumors of considerable size and weight, sometimes pedunculated.

There is a familial and hereditary tendency, with involvement of the ectodermal layers. Yakooler and Guthrie employed the term "congenital ectodermatosis" to describe the lesion.

The first manifestations may be seen at birth or early in life, but the tumors at the time are usually small and grow only very little, so to speak parallel with the growth of the body. About the age of puberty the growth may become accelerated and only then do symptoms appear. At times the disease may be advanced during childhood, as in this case.

As mentioned, the symptoms are due mostly to pressure of the growing tumor on the neighboring organs. Thus tumors on the spinal nerve roots will compress the spinal cord. Neurofibromata arising from the cranial nerves will eventually produce symptoms of increased intracranial pressure, cerebellar symptoms, eighth nerve symptoms, etc. The tenth and the fifth nerves are frequently involved. It is therefore important to pay attention to the pigmentation of the skin and other localization of tumors on peripheral nerves in order to avoid an error in diagnosis. Unfortunately for the diagnosis not all cases show the combination of cutaneous and central symptoms.

The hereditary element in the syndrome manifests itself by various congenital defects such as spina bifida occulta or malformation of fingers. Kyphoscoliosis is common. Subperiosteal neurofibromas may produce symptoms resembling bone cysts. Mental defects can be the effect of central tumors; at times they may be referable to congenital anomalies. But as a rule the mental condition is normal.

Operative procedures are only necessary if the location of the tumor warrants them. Intracranial tumors are frequently multiple and usually cannot be completely removed. Great pain or disability may make operation necessary. X-ray and radium treatment are not satisfactory.

The prognosis of the disease for life is relatively poor. Only intracranial lesions are serious, as mentioned, on account of their location and because they are almost always multiple and cannot be completely removed.

# EXCISION OF TERATOMA OF THE ANTERIOR MEDIASTINUM<sup>1</sup>

HAROLD NEUHOF, M.D.

## CASE REPORT

*History* (Adm. 465512). E. S. a two year old girl had been a feeding problem. In February and March of 1940 she was examined by her family physician because of irritability. At that time fluoroscopy of the chest was negative. The child was well in June. Early in July 1940 there began fever, cough, abdominal and also thoracic pain. Since that time there were episodes of abdominal distress, thoracic pain, and transient fever. Temperature was not taken at frequent intervals so that a temperature of 102°F. which was found to be present in the physician's office in mid August, 1940, was not suspected to have existed. After mid August the temperature was taken at regular intervals. It was found that there was a persistent, irregular, low-grade fever. After an early phase in which there was some loss in weight there was a later phase in which the weight was regained. Numerous blood counts did not suggest suppuration. The range in hemoglobin was from 70 to 90 per cent. Beginning some time in August, 1940, there were short episodes of unproductive cough which became more frequent in September. In August and September several series of films of the chest were made. All revealed an area of opacity in the left mid-thoracic region (fig. 1). Lateral films indicated that the shadow occupied the anterior thoracic field. Thus, the history and the films pointed essentially to a low grade intrathoracic infection.

The child was admitted to The Mount Sinai Hospital on October 25, 1940, as an emergency on the assumption that she was suffering from a chronic pleural infection with a more recent flare-up.

*Examination:* The findings were essentially negative except for signs of an anterior encapsulated pleural effusion. Aspiration was done in the second and third anterior left interspaces. From both spaces cloudy fluid was withdrawn which contained some grumous material.

*Operation:* Operation was performed by excision of a liberal section of the anterior portion of the third rib. There was at once revealed a tumor which arose from the anterior mediastinum. It was covered by a thick inflammatory membrane. At first the lung was not seen and also it was noted that there was some clear fluid in the free pleural space. Upon further examination the tumor was found to be adherent to the lung both above and below, as well as posteriorly. It was adherent intimately by inflammatory tissue as well as by fibrous tissue to the pericardium and the great vessels. Laterally there were adhesions to the parietal pleura and thoracic parietes. The problem which was encountered at operation was to find a plane of cleavage for the complete removal of the mass. This was not easy because of the inflammatory reaction, and sharp resection was required for the release of the tumor. After the complete removal of the tumor the incision in the thoracic wall was closed in layers and air was withdrawn from the pleural space by means of a pneumothorax apparatus.

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

*Course:* The operative procedure was a shocking one and transfusion of blood was required. The postoperative course was uneventful except for an effusion of blood into the pleural space which was withdrawn the day after operation.

*Surgical pathology:* The gross appearance of the tumor was strongly suggestive of a teratoma. The mass was 6 x 3 x 3 cm. after its contents had been evacuated. The latter was grumous material. The surface of the mass was smooth for the most part and of a grey-red color. The inner surface was completely irregular presenting yellowish-red projections, some of which were polypoid and at other places had the appearance of skin. A number of short white and grey hairs projected from the lining membrane.

The microscopic examination revealed the picture of teratoma without any evidence of malignancy. A portion of thymic tissue was attached to the tumor.

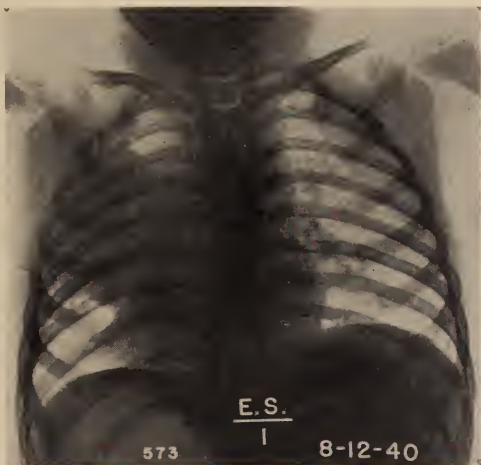


FIG. 1. X-ray film showing a large sharply demarcated shadow in the left chest which appears to be situated either in the lung or in the pleura and does not suggest a mediastinal tumor. (In the lateral view the density was hemispherical and was situated anteriorly.)

*Follow-up;* It is now 2½ years since operation. The child has gained 30 pounds. X-ray examination of the chest is negative and the general health is entirely satisfactory.

#### COMMENT

Compared with the problem of malignant teratoma which is by no means infrequently encountered in adults the problem of the removal of a teratoma in a child is surely a much simpler one. Accordingly, this case points clearly to the eminent desirability of removing mediastinal teratomata in childhood even in the absence of any clinical manifestations referable to the neoplasm.

# CERVICOMEDIASTINAL LYMPHANGIOMA (CYSTIC HYGROMA)<sup>1</sup>

## REPORT OF TWO CASES IN INFANTS

ERNEST E. ARNHEIM, M.D.

[From the Surgical Service of Dr. Harold Neuhof]

Cystic hygroma of the neck is a well-known disease entity of infancy and childhood, and approximately 225 cases have been reported to date. These tumors have been described in locations other than the neck, as in the axilla, the chest wall, the groin, and in the retroperitoneum, but the cervical lesions are by far the most common. Although some authors (Gross and Goeringer (2)) have stated that cystic hygromas of the neck may extend into the mediastinum, a review of the literature revealed only 3 individual case reports in which there was involvement of both the neck and the mediastinum (Goetsch (1), Michaelis (4), and Martin and Lelong (3)). Two cases of cervicomediastinal lymphangioma (cystic hygroma) in infants are reported in this communication.

### ETIOLOGY

In order to understand fully the origin of cystic hygroma of the neck, the basic embryologic facts of the development of the lymphatic system of the neck must be outlined (Sabin (5)). In the first stage of development of the lymphatics, a capillary plexus is formed from the jugular vein on each side. Some of these capillaries are cut off from the parent vein and coalesce to form sacs on either side of the neck lateral to the primitive jugulars. The secondary stage of development consists of the growth of lymphatic vessels by endothelial sprouts derived from the lining of the jugular sacs. These lymphatic vessels coalesce and become a unified system which later acquires permanent communications with the venous system.

Through some anomaly, some of these lymphatic channels may become pinched off or sequestered and fail to establish a communication with the venous system. This sequestered lymphatic tissue may retain the power of growth inherent in the process of endothelial sprouting and give rise to the lesion known as cystic hygroma.

### PATHOLOGY

Hygroma is a multilocular (occasionally monolocular) cystic tumor, the cavities of which are lined by endothelium. The fluid content of the cysts is usually clear or straw-colored, occasionally turbid or blood-stained.

Goetsch (1) has given histologic evidence explaining the manner of growth and development and the destructive action of these tumors. According to Goetsch, endothelial fibrillar membranes or sprouts from the walls of the marginal cysts penetrate the adjacent tissues. A lymph-like fluid is secreted within the fibrillae,

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

which are thus canalized forming minute cysts with an endothelial lining. By continued secretion within the cysts enlarge; by pressure atrophy of the walls between adjoining cysts, larger cavities are formed. By this process of infiltration of endothelial sprouts the surrounding tissues are destroyed, either by direct atrophy and fatty degeneration, or by being disintegrated in the cystic fluid which is formed around them. While this microscopic destruction of tissue is going on, the growing tumor increases the pressure exerted by its walls, and the extension and penetration of the marginal cysts cause damage to surrounding structures. The rapidity of growth may be that of a malignant tumor, but there is no evidence that the tumor is a malignant one. On meeting a barrier such as a large muscle or blood vessel, the cysts surround it in a saddle bag fashion and supply it with an endothelial covering which is continuous with the lining of the surrounding cyst.

#### CLINICAL FEATURES

Cystic hygromas of the neck occur most frequently in the posterior triangle, lying behind the sternomastoid muscle in the supraclavicular fossa; occasionally, the cyst may occupy the anterior cervical triangle. In rare cases, the tumor may completely fill the entire side of the neck. A varied extent of invasion of the mediastinum may occur, usually the superior mediastinum, but occasionally extending below this level. In one of the cases reported in this communication, the tumor reached the level of the eighth thoracic vertebra.

In the majority of cases, the tumor in the neck is first noticed at birth, and the size of the mass does not bear any relationship to the duration of the lesion. The ages of the patients in this communication were 15 months and 17 months. Males and females are about equally affected.

With invasion of the mediastinum, symptoms due to pressure on adjacent structures may be noted occasionally. Respiratory embarrassment in one of our cases, due to pressure on the trachea, was so marked that the appearance of the infant was similar to that noted in traumatic asphyxia.

The small lesions in the neck appear as single masses with smooth contours, but in the larger tumors faintly lobulated surfaces may be seen. The masses have poorly defined borders and are not tense. The overlying skin is usually normal, but may appear slightly bluish. The masses can be transilluminated.

Roentgen examination of the cervical mass shows a soft tissue swelling. It is this examination, however, which is diagnostic of mediastinal involvement. The roentgen findings will be discussed in more detail in the case reports. In addition to the visualization of the mediastinal tumor, the roentgen examination may aid in showing lateral displacement of the trachea or forward displacement of the upper esophagus.

Cystic hygromas of the neck may occasionally be confused with bronchial cysts or lipomas, and the lesions in the mediastinum are to be differentiated from other tumors of the mediastinum, principally dermoid cysts and teratomas, ciliated epithelial cysts, lipomas, and tumors of the thymus. The mediastinal tumor presents more of a problem in diagnosis than the cervical tumor, but the

combination is diagnostic of cervicomediastinal cystic hygroma in infancy and childhood.

#### TREATMENT

Although one may temporize in the treatment of cystic hygroma of the neck (and this is not advised), the so-called "expectant" treatment has no place in the therapy of cervicomediastinal hygroma. The growth of these tumors in the mediastinum will, sooner or later, result in pressure on important structures which will necessitate urgent relief. Considering the pathology and location of the lesion in the mediastinum, complete excision of these tumors is hardly feasible. However, partial excision in our cases and in those of Goetsch, and Martin and Lelong, has resulted in marked relief of symptoms. Goetsch has employed roentgen therapy of the mediastinal component after excision of the cervical lesion, and reported almost complete disappearance of the mediastinal extension.

#### REPORT OF CASES

*Case 1. History* (Adm. 374202). T. B., a male infant, aged 1 year and 5 months, was admitted to The Mount Sinai Hospital on December 3, 1934, with the history of a swelling in the lower anterior part the right side of the neck. In the month prior to admission, the swelling rapidly increased in size to such an extent as to inhibit movement of the head downward on that side.

*Examination.* The temperature was 102.6°F., the pulse 180, and respirations 56 per minute. There was a rounded, large, cystic mass in the lower right anterior cervical triangle of the neck. There was some respiratory distress, but no marked dyspnea or cyanosis.

A roentgenogram of the chest (fig. 1) revealed a mass occupying the mesial two-thirds of the upper half of the right side of the thorax. The trachea was displaced considerably to the left.

*Operation.* Operation was performed by Dr. Harold Neuhof on the day of admission, under ether anesthesia. A horizontal incision was made over the mass in the neck. The right sternomastoid, sternothyroid, and sternohyoid muscles were divided. The multi-locular cystic tumor was gradually exposed. The walls of some of the cysts were thin and translucent, and others more fibrous. The phrenic nerve was intimately attached to the walls of the tumor and separated from it. The carotid sheath seemed to form a part of the wall of the tumor and the dissection partly entered the sheath. The internal and external jugular veins were divided and ligated. The roots of the cervical plexus of nerves were attached to the tumor by fibrous tissue and dissected free. After a difficult dissection and exposure of the posterior wall of the tumor, it was found that, over an area about 3 cm. in diameter, the wall of the tumor was intimately incorporated with the prevertebral musculature, and the cervical portion of the tumor was excised leaving a portion of the posterior wall.

The superior mediastinum was entered along the anterior surface of the presenting portion of the mediastinal tumor. The mass was gradually dissected free, exposing the innominate artery and the junction of the right subclavian and common carotid arteries. When this stage of the dissection was reached, air was noted to escape directly back of the innominate artery, being air sucked in and out of the mediastinum. Since the tumor extended beyond this area toward the pericardium, it was evident that further excision of the tumor would be too hazardous an undertaking. Accordingly, the walls of the exposed cysts were excised with an escape of straw-colored fluid. The remnants of tumor in the neck and the mediastinum were painted with a 5 per cent solution of sodium morrhuate.

A strip of iodoform gauze was placed into the mediastinum and brought out at the posterior angle of the incision. The divided sternomastoid and ribbon muscles were united and the subcutaneous tissues and skin were closed.

*Course.* The infant withstood the operative procedure well. The temperature was elevated to 102°F. for four days, and the pulse and respiratory rate became slower. The packing was gradually shortened and was out by the fifth postoperative day.

Roentgen examination of the chest, one week after operation (fig. 2) revealed a mass in the upper half of the right thorax, perhaps a little smaller than on the preoperative x-ray examination. The deviation of the trachea to the left was not as marked, but it was still beyond the median line. A small collection of air was seen in the mediastinum.



FIG. 1. Roentgenogram of the chest on admission showing a mass occupying the mesial two-thirds of the upper half of the right side of the thorax, with marked displacement of trachea to the left.

The infant was discharged from the hospital, with a healed wound, 11 days after operation. The pathological report of the tumor was hygroma cysticum with acute inflammation.

Follow-up examinations, over a period of 8 years, showed a gradual reduction in the size of the mediastinal roentgen shadow, and no recurrence of the cervical component. Roentgen examination of the chest 2 years after operation (fig. 3) revealed a marked reduction in the size of the mediastinal mass. The trachea was now in the midline.

*Case 2. History* (Adm. 389705). T. C., a female infant, aged 1 year and 3 months, was admitted to The Mount Sinai Hospital on February 7, 1936, with the history of a swelling in the left side of the neck since birth, progressively increasing in size. About 6 months before admission an x-ray examination of the chest showed the presence of a tumor in the mediastinum. At that time, however, there were no symptoms. Dyspnea and cyano-



FIG. 2. Roentgenogram of the chest, 1 week after operation, showing a mass in the upper half of the right thorax, with less deviation of the trachea and a small collection of air in the mediastinum.

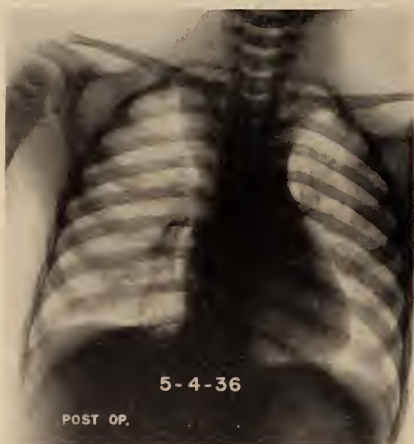


FIG. 3. Roentgenogram of the chest, 2 years after operation, showing marked reduction in the size of the mediastinal mass, with the trachea in the midline.

sis were noted about 5 days before admission, steadily increasing, so that for 2 days the child could not lie down because of respiratory embarrassment. Swelling of the upper eyelids was noted on the day before admission.

*Examination.* The temperature was 99.8°F., the pulse 152, and respirations 146 per minute. There was marked cyanosis of the skin of the head, neck, and upper chest, an appearance similar to that seen in traumatic asphyxia, particularly in regard to the purplish hue of the cyanosis. Dyspnea was marked, and the child could breathe only in a sitting-up position. There was an enormous collar-like swelling of the left side of the neck, extending from the ramus of the jaw down to and slightly overlapping the clavicle. There was dullness to flatness on percussion over the left anterior chest wall.



FIG. 4. Roentgenogram of the chest on admission showing a large mediastinal mass reaching to the level of the eighth thoracic vertebra, with marked displacement of the trachea to the right.

A roentgenogram of the chest (fig. 4) revealed a mass extending down from the neck into the superior and anterior mediastinum reaching to the level of the eighth thoracic vertebra. There was marked displacement of the trachea to the right. In the lateral view there was posterior displacement of the trachea.

*Operation.* Operation was performed by Dr. Harold Neuhoef immediately after admission. Inhalation anesthesia was not employed because of the risks involved, and the child was held in a sitting-up position. A transverse incision was made just above the left clavicle. The thinned-out sternomastoid muscle was divided. A large cyst was entered and clear straw-colored fluid evacuated. Other cysts were opened and in one of them a collection of bloody fluid was found. In view of the fact that the purpose of operation was relief from asphyxia, those encapsulations were entered which appeared to compromise the trachea. These cysts, 6 or 7 in number, presented fleshy intervening septa.

The latter were partly excised for the purpose of converting separate loculations into a communicating pathway. After a few of the lower cervical encapsulations were entered, the trachea could be felt and there seemed to be some approach of the trachea to the median line.

A large cyst in the superior mediastinum was entered leading to a space behind the sternum and the first 3 ribs, the finger dipping down back of the ribs to terminate at the bottom of the space about the level of the pericardium. The limits of this space were mesially the midline, and posteriorly the hilum of the left lung and the aorta. The interiors of the lower cervical and mediastinal membranes were swabbed with a 5 per cent solution of sodium morrhuate. Strips of iodoform gauze were placed in the mediastinum and lower cervical regions, and the skin was closed. At the termination of operation the child could lie flat without respiratory difficulty.

*Course.* The infant withstood the operative procedure well. The temperature was elevated to 104°F. on the first postoperative day, thereafter gradually falling to normal. The packings were gradually shortened and were out by the fourth postoperative day. The infant was discharged from the hospital 5 days after operation.

The pathological report of the tumor was hygroma cysticum.

*Second admission.* The child was readmitted to The Mount Sinai Hospital on March 11 1936, 1 month after operation. There had been a reduction in size of the swelling of the neck after operation, but soon thereafter the swelling increased in size.

*Examination.* The temperature was 100.4°F., the pulse 136, and the respirations 28 per minute. There was a large soft swelling in the left submaxillary region extending down to the level of the cricoid cartilage.

Roentgen examination of the chest revealed a reduction in size of the mediastinal mass, and the trachea was nearer to the midline.

*Operation.* Operation was performed by Dr. Harold Neuhof on the day of admission, under ether anesthesia. A transverse incision was made over the mass in the neck. A large, multilocular, cystic mass was partially excised, and the interior of the cavity swabbed with a 5 per cent solution of sodium morrhuate. The skin was closed.

Aspiration of the chest in the second intercostal space to the left of the sternum was performed, and fluid was readily withdrawn. About 20 cc. of the fluid were withdrawn and replaced by an equal amount of 5 per cent solution of sodium morrhuate.

*Course.* The temperature was elevated to 101.8°F. on the first postoperative day. The child was discharged two days after operation.

#### SUMMARY

The embryologic, pathologic, and clinical features, and the treatment of cervicomediastinal lymphangioma (cystic hygroma) are reviewed.

Two cases of this condition in infancy, the fourth and fifth in the literature, are reported.

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## ADENOMA OF THE BRONCHUS<sup>1</sup>

HERMAN HENNEL, M.D.

This case report is of interest for the following reasons: It represents one of the youngest patients on record with bronchial adenoma; the adenoma in this instance is of the rarer variety as regards size and location; it illustrates the clinical features and course as observed over a period of more than eight years; it presents an interesting and also difficult therapeutic problem.

### CASE REPORT

*History* (Adm. 483274). E. S., a boy aged 17 years, was first admitted to The Mount Sinai Hospital on December 17, 1941 with hemoptysis, chest pain, dyspnea, cyanosis and fever of five days' duration.

The patient stated that he first came under medical observation for pulmonary complaints at the age of nine years with cough, right chest pain and an acute febrile episode lasting about four weeks. Roentgenographic examination at that time revealed a circumscribed mass in the right paratracheal region which was interpreted by competent European observers as representing a mediastinal neoplasm. The child made an uneventful recovery from the acute illness, but the shadow in the chest remained unchanged. During the succeeding years the boy experienced numerous similar acute febrile episodes of varying severity, on the average of once every 1-2 years, lasting 3-5 weeks, from which recovery was always uneventful. During the long periods intervening between the separate acute episodes the boy was apparently in good health and was able to carry on normally. However, on careful questioning he admitted that he has had a slight choking cough as long as he could remember.

In December 1941, five days before admission to the hospital, the patient was exposed to inclement weather for many hours. When he returned home that evening he felt feverish, developed an annoying cough and had severe right lower chest pain made worse by coughing. The following day he began to cough up mouthfuls of bright red blood. Soon thereafter the pain in the chest became more acute, and shortness of breath became increasingly more distressing. As the symptoms grew worse during the ensuing days he sought admission to the hospital on the fifth day of his illness.

*Examination.* On admission to the hospital the patient appeared acutely ill. He had marked dyspnea, moderate cyanosis, he coughed at frequent intervals bringing up mouthfuls of bright red blood, and he complained of severe right lower anterior chest pain. His temperature was 101°F. His pulse was rapid but of good quality. The chest showed marked diminution of motion of the right hemithorax. There was almost complete dextrocardia. There was markedly impaired resonance, diminished to absent breathing, and increased tactile fremitus over most of the right lung. These signs indicated atelectasis of the right lung with mediastinal displacement to the right. The left lung appeared normal. These findings were confirmed by x-ray examination of the chest on admission.

*Laboratory data.* Blood: hemoglobin 73 per cent; 12,600 white blood cells with 75 per cent polymorphonuclear leucocytes. Urine: no abnormal findings. Tuberculin test was negative in the usual concentrations. Examination of the sputum showed no tubercle bacilli. Sedimentation time was normal. Circulation studies showed no abnormalities. The electrocardiogram showed T<sub>2</sub> diphasic and T<sub>3</sub> inverted, apparently due to the cardiac displacement to the right.

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<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

*Course.* The clinical features in the case suggested the diagnosis of adenoma of the bronchus, with bleeding, and aspiration of blood into the bronchi of the right lung with resultant atelectasis of that lung. Whether there was an associated pneumonitis was not clear. Bronchoscopic examination was indicated in order to establish the diagnosis, to remove the obstructing adenoma if one was found, and to aspirate the retained blood clots and thus relieve the atelectasis. This was done shortly after admission to the hospital. The first bronchoscopic examination was unsatisfactory because of brisk bleeding from the adenoma which prevented adequate visualization of the various structures. A tumor mass was seen in the right main bronchus at about the level of the opening of the right upper lobe bronchus from which material for biopsy was obtained. This biopsy, as well as several others taken on subsequent occasions, was reported by the pathologist as typical of bronchial adenoma, namely, alveolar arrangement of small regular cells which showed no mitosis and stained evenly.

During the first bronchoscopic examination an attempt was made to control the bleeding by cauterization and to aspirate the blood clot in order to relieve the atelectasis. This was partially successful but only for a short time. Immediately after bronchoscopy physical and roentgen-ray examination showed considerable reexpansion of the right lung. However, complete atelectasis recurred within twelve hours, apparently as the result of further bleeding.

During the ensuing few days the bleeding from the adenoma stopped and the patient's condition improved rapidly. After several bronchoscopic aspirations of the blood clots in the bronchi the lung reexpanded and eventually the roentgen appearance was essentially the same as that seen on the film made three years before, the earliest available film.

While the diagnosis of bronchial adenoma was established by histologic examination of several biopsy specimens, the precise location and extent of the tumor with relation to the involved bronchus could not be established with any degree of certainty despite numerous bronchoscopic studies over a period of many months. It was the impression of the bronchoscopist that the adenoma was of unusual size; that it apparently occluded the orifice of the right upper lobe bronchus so that its lumen could not be visualized; that it in some way injured the wall of the right main bronchus so that the wall tended to collapse. Repeated attempts to remove the adenoma and to reestablish a patent bronchial lumen were unsuccessful. It was the final opinion of the bronchoscopist (Dr. Rudolph Kramer) that further bronchoscopic manipulations would be of no avail and were, therefore, not justified.

The patient left the hospital in March 1942 and has been closely observed in our follow-up clinic since his discharge awaiting a final decision concerning further therapeutic procedures.

#### DISCUSSION

Apparently this case belongs to the smaller group of bronchial adenomas which, because of their size and the extent of involvement of the bronchi, are not susceptible of bronchoscopic removal. They require lobectomy or pneumonectomy for cure.

The question arose whether the shadow seen on the film represented a huge adenoma or whether it represented an atelectatic right upper lobe which resulted from complete obstruction by an adenoma of the usual small size. Ordinarily the bronchoscopic examination can furnish a definite answer to this question, but this was not possible in this instance. An attempt was made to obtain this information by contrast visualization of the pulmonary vessels to the various lobes of the right lung, but the result of this examination was inconclusive. Angiography showed the right pulmonary artery to be decidedly narrower than the

left and the right pulmonary branches showed poor visualization as compared with the excellent contrast visualization of the arterial branches in the left lung. This was particularly true of the arterial branches in the right upper lobe where delay in the clearing of the opacification was also noted.

Another approach to this problem could possibly be by bronchography. We have so far refrained from employing this method for fear of introducing infection beyond the point of obstruction.

The question of correctly interpreting the nature of the shadow on the film is not merely of academic interest, but is of clinical importance as it may determine the issue of operative intervention. This shadow may represent an atelectatic right upper lobe as already suggested; or it may represent the tumor which is located within a dilated branch of the right upper lobe bronchus. For both these conditions lobectomy would be an adequate procedure. But if the shadow represents the intramural type of bronchial adenoma, the type which penetrates the wall of the bronchus toward the mediastinal surface, only pneumonectomy would suffice for cure. While one may be inclined to perform a lobectomy in this type of case, one would hesitate to resort to the more radical procedure of pneumonectomy.

As is now well known, adenoma of the bronchus is a serious lesion because of its tendency to produce bronchial obstruction with infection beyond the point of obstruction, namely, recurring pneumonitis, suppurative disease of the lung and bronchi, pleural infection. While some patients may escape this complication for many years, it is bound to occur earlier or later, and frequently with disastrous results. We are therefore, confronted in this case with two alternatives: the potentially serious consequences of the persistent bronchial obstruction, and a potentially serious surgical procedure.

The choice is not an easy one. We now favor radical surgical intervention because of the following considerations: 1) The past history of recurring acute episodes of increasing severity; 2) the danger of persisting infection which would greatly increase the difficulties of operative intervention; 3) the youth of the patient, his good general condition, and freedom from infection at the time operation is contemplated which constitutes the optimal condition for successful surgery.

Whether a lobectomy would be adequate or a pneumonectomy would be required can only be determined after an exploratory operation. It is most probable that the more radical procedure (pneumonectomy) will be required for a cure.

## A CASE OF CERVICO-THORACIC NEUROFIBROMATOSIS<sup>1</sup>

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Aside from the risks inherent in the nature of neurofibromatous tumors, the disease has a striking morbidity especially when it involves the thorax.

Early thoracic involvement may completely escape recognition. However, when the tumor assumes considerable proportions, complications may arise from pressure on important structures. Such symptoms as thoracic pain, cough, dysphagia, dyspnea, and cyanosis may present themselves, and generally indicate an advanced stage of the disease.

The following case emphasizes these points, and calls attention to the importance of carefully observing the chest in cases suggesting the diagnosis of neurofibromatosis.

### CASE REPORT

*History* (Adm. 421784). A. B., aged 4 years, was admitted to The Mount Sinai Hospital on March 23, 1938. The child was apparently normal at birth, except for a few scattered pigmented areas about the body. At the age of 3 weeks, the mother first noted a mass on the scalp, which increased in size. At the age of 7 months, a private physician treated the mass with x-ray, with resulting depigmentation.

At the age of 10 months (February, 1935) the child was taken to the Post-Graduate Hospital because of a lump in the side of the neck, which had steadily increased in size. A biopsy of this mass was performed, and a pathologic diagnosis of neurofibromatosis made. X-ray examination of the neck and chest at this time revealed a swelling in the submaxillary region, involving the soft tissues of the retrolaryngeal and retrotracheal areas. The tracheal shadow was already narrowed, with widening of the superior mediastinum. This was interpreted as thymic enlargement, for which the child received x-ray therapy without significant change in his symptoms or x-ray findings.

In April 1937, when the child was 3 years old, he was admitted to Babies Hospital for investigation. An irritating cough was present. Examination revealed a soft tissue swelling in the right occipital region, with several smaller adjacent firmer masses. A large mass was felt in the right side of the neck. There was considerable brownish pigmentation below the ear, the right cheek and the front of the neck. Over this area, there was a growth of fine white hair. A few scattered pigmented areas about the body were also present. The liver and spleen were not palpable. The heart and lungs were normal. There were no significant abnormal neurologic findings. The white blood count was 13,200 with 68 per cent polymorphonuclear cells, and 27 per cent lymphocytes. X-ray examination of the chest showed distinct widening of the superior mediastinum. There were soft tissue masses in both sides of the neck, which seemed to extend into the superior mediastinum.

X-ray examination of the skull showed no increased density within the cranium, but showed sclerosis of the parietal bones, more marked on the right.

The child remained in the hospital for 22 days. A biopsy of the neck mass at this time was reported as neurofibroma.

The child received radiotherapy for 2 weeks, and the impression was that the neurofibroma was reduced in size. The persistent cough seemed to be somewhat improved.

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

After several weeks the child was discharged from the hospital and was followed in the out-patient department receiving radiotherapy for several months, until December 1937.

In March 1938, 1 week before admission to The Mount Sinai Hospital, the child had fever, cough, and increasing dyspnea. During the 24 hours before admission, he became cyanotic, and his respiratory distress became marked.

*Examination.* On admission the boy appeared pale, chronically ill, with marked stridor, cyanosis and dyspnea. The temperature was 103°F. An irregular lobulated soft mass extending from the right occipital region forward beneath the right side of the neck was felt. The skin over the chest was thrown into folds and was pigmented. There were irregular areas of brownish pigmentation scattered over the entire body. The chest showed rachitic deformity and scoliosis, and the respiratory excursion was limited. Breath sounds were diminished bilaterally; there was dullness over the right upper chest; numerous coarse



Fig. 1. Postero-anterior view: Multilobular shadows which appear to spread outward from the mediastinum. The trachea is compressed.

and medium râles were scattered throughout both lungs. The heart rate was rapid, but otherwise normal.

X-ray examination of the chest showed a huge mass in the superior mediastinum, compressing the trachea laterally (fig. 1). There was widening of the retro-tracheal space at the base of the neck, due to upward extension of the mediastinal mass (fig. 2). There was an infiltration in the right upper lobe, with scoliosis of the dorsal vertebrae. The blood count revealed 19,200 white blood cells with 87 per cent, polymorphonuclear leucocytes, 14 per cent of which were non-segmented; 14 per cent lymphocytes, and 4 per cent monocytes.

*Course.* Direct laryngoscopy was performed and showed bulging of the retropharyngeal tissues. The larynx was normal; the trachea was narrowed. There was a large amount of thick non-purulent secretion in the trachea, which was suctioned without relief to the



FIG. 2. Lateral view: There is extreme anterior displacement of the trachea as seen in cervicomedialastinal abscess.



FIG. 3. Photograph of autopsy specimen, showing extensive involvement of mediastinal tissues, more marked on the right.

child. Therefore a bronchoscope was passed. But this procedure was of no avail. On removal of the bronchoscope, the child was unable to breathe. The bronchoscope was reinserted, and tracheotomy performed.

The condition of the patient was very poor, and in spite of heroic measures, he ceased shortly thereafter.

*Summary of post-mortem findings.* There was diffuse patchy pigmentation of the skin, and atrophy of the right side of the face and skull were present. Evidence of diffuse neurofibromatosis was present macroscopically and microscopically (fig. 3). This involved the sympathetic chain, the splanchnic nerves, the solar, hepatic, and suprarenal plexuses, the vagi, hypoglossal, spinal accessory, glossopharyngeal, and lingual nerves. Similarly involved were the right brachial plexus, the occipital and cutaneous nerves of the neck, the phrenic nerves, the nerves of the heart, lungs, thymus, liver, gall-bladder, pancreas, adrenals, the mesentery of the ileum, and the rectum. Intramural tumor-like infiltration of the heart was present. There was a mild atheromatosis of the anterior mitral leaflet, and of the ascending aorta. The status post-tracheotomy and post-bronchoscopy was noted, and also scars of the previous biopsies of the neck, and the suboccipital region.

The immediate cause of death was a purulent bronchitis and bronchopneumonia.

#### COMMENT

This case illustrates the character of neurofibromatosis, especially as it involves the cervico-thoracic region. The extensive involvement, as noted from the autopsy findings, is unusual. When the symptoms of respiratory distress appeared, the disease was well advanced, and could be little influenced by therapy. This is not an uncommon attribute of neurofibromatosis, especially when it affects the mediastinum.

Neurofibromatosis is a disease of particular interest in childhood, since its striking incidence in early life, its frequent association with congenital abnormalities, and its familial character have caused it to be considered as a congenital anomaly of the ectoderm. The presence of bony changes suggest mesoblastic involvement as well. Considerable literature has been devoted to a discussion of the embryologic origin of the disease, without final solution. Whatever the origin, however, few diseases present such extensive involvement, and as a result, such striking clinical variation.

The disease may involve the skin and subcutaneous tissues, the visceral organs, the endocrine glands, and the bones. The symptoms presented depend on the extent and nature of the organs involved.

Thoracic neurofibromatosis is rare, as are all intrathoracic tumors of neurogenic origin. The literature contains relatively few reports of this type of intrathoracic tumor. Many reports do not distinguish between neurofibroma and other neurogenic tumors, such as ganglioneuromas. This can easily be understood, since the distinction is at times impossible. Epstein (1) presented a case of intrathoracic neurofibroma in a 4 year old child, which to a degree, resembled the case here presented. Operative removal of the tumor did not interfere with its continued growth. Epstein indicated that up to 1937, only 24 cases of intrathoracic tumors of neurogenic origin had been reported, of which one-half were described as ganglioneuromas.

Mediastinal neurofibromas arise from the sheath of the thoracic nerves, or the paravertebral sympathetic trunks. Cervical neurofibromatous masses arise

from analagous structures in the neck, and may consist of an extension of the intrathoracic process, as it did in our case.

The clinical features depend on the location, the size, and origin of the tumor. Several forms have been described. The so-called hour-glass type of tumor may arise from the spinal nerves, or the fibrous structures of the vertebral canal, and extend into the mediastinum; or they may arise from thoracic structures, and extend into the vertebral canal. This capacity to extend from the spine into the mediastinum or vice versa, is important, since this may determine the presenting symptoms. When the tumor extends into the spine, it may produce symptoms of cord compression. When the tumor is predominantly thoracic, the symptoms may be essentially thoracic. Both types of symptoms can occur. Of 13 hour-glass tumors collected by Heuer (2) 11 presented outstanding symptoms of cord compression.

Intrathoracic neurofibromas are usually found in the posterior mediastinum. In a general way, they give few symptoms until the disease is well advanced. Pain, cough, dyspnea, and symptoms of compression of mediastinal structures usually present themselves after the tumor has been present for a considerable time. Pain radiating along an intercostal nerve may be an early and presenting symptom when neurofibroma of the intercostal nerve is present. In this event, erosion of the adjacent ribs may be demonstrable on x-ray.

The x-ray features of neurofibromatosis have been much discussed. There are some who consider them diagnostic. According to Lenk (3) the x-ray reveals a large, homogeneous, sharply defined lesion with a curved border. The long diameter parallels the spine. Usually the lesion is asymmetrical. It has a broad base, which in the lateral view partially covers the body of the vertebra. There may be evidence of pressure on adjacent bony structures.

Neurofibromas must be differentiated from other tumors of the posterior mediastinum, such as fibromas, ganglioneuromas, chondromas, etc. Frequently this is possible only at the operating table. Occasionally aspiration of tumor tissue and identification of tumor cells has been successful, but this procedure has its risks. Biopsy of available masses are of course of important diagnostic value. The ganglioneuroma is more apt to fill the left upper posterior mediastinum, and more frequently gives rise to a Horner syndrome. This however is not of final diagnostic importance.

As in other parts of the body, neurofibromas of the mediastinum may undergo malignant degeneration. Fischer (4), in his review of collected cases, reported this incidence as 13 per cent. This coincides with the usual estimate. When malignant degeneration occurs, metastases to the ribs, the lungs, and the vertebral bodies may take place. These usually occur late, and according to Hosoi (5) in about 22 per cent of the malignant cases.

The treatment of neurofibroma of the mediastinum is essentially surgical, if the tumor is discovered before it has attained great size or has undergone malignant change. Andrus and Heuer (6) quote Harrington as having reported 14 cases, with 2 operative deaths, and 1 death  $2\frac{1}{2}$  years after operation, from recurrence of a malignant tumor. If operation is performed early, the prognosis is

considered good. Of the 13 cases of hour-glass tumors collected by Andrus and Heuer, 9 were subjected to laminectomy because of presenting cord symptoms; 5 of these recovered, 4 died. Undoubtedly, the choice of approach to the tumor, its size and characteristics, the surgeon's technique and dexterity, are factors which play a role in the final prognosis. It has been noted in some cases that inadequate surgical excision or extirpation of the tumor may activate malignant metaplasia. Once this occurs, the prognosis is bad.

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# HUGE GANGLIONEUROMA OF THE MEDIASTINUM<sup>1</sup>

COLEMAN B. RABIN, M.D.

## CASE REPORT

*History* (Adm. 467829). The patient, aged five years, was admitted to The Mount Sinai Hospital on February 1, 1940. Six months previously a murmur was heard over the precordium and an x-ray examination, performed to determine the size of the heart, disclosed a tumor in the left chest. Except for the occurrence of a bilateral squint and myopia he had developed normally and he had had no infectious diseases aside from whooping cough. The family history was irrelevant.

*Examination.* The child was well nourished and developed. There was a slight squint, but the pupils were equal and there was no ptosis or enophthalmos. The right testicle was not palpable. The upper left chest was protuberant and the supra- and infraclavicular fossae on this side were obliterated and slightly bulging. The veins of the left upper chest and of the left arm were prominently distended; the latter did not collapse on raising the arm above the head. There was flatness over the upper half of the left chest with marked diminution of breath sounds and tactile fremitus over this area. The trachea was deviated to the right and there was a systolic thrill over the vessels at the base of the right side of the neck. A loud systolic bruit was audible in this region and also over the base of the heart. At the cardiac apex this was also audible, but not as loud. The bruit was clearly heard in the interscapular region. The pulsations of the axillary, brachial and radial arteries were normally palpable on the right side, but pulsations could not be detected in any of these vessels on the left.

*Laboratory data.* The blood pressure readings were as follows: Right arm 108 systolic and 74 diastolic; right leg 110 systolic and 78 diastolic; left leg 108 systolic and 74 diastolic. No readings were obtainable in the left arm. The blood count was normal. Roentgenographic examination of the chest disclosed a large lobulated mass in the upper left chest, extending from the apex to the level of the seventh rib posteriorly (fig. 1). The uppermost ribs were spread apart and the posterior part of the second rib was markedly thinned apparently as a result of pressure atrophy. The trachea was displaced to the right and the left main bronchus was displaced downward and to the right by the tumor. On the oblique and lateral views particularly, the sharp demarcation of the borders of the lobulated tumor was clearly evident, and on these views it could be seen that the neoplasm was situated mainly posteriorly (fig. 2).

*Diagnosis.* Because of the sharp demarcation of the mass and the evidence of pressure atrophy rather than invasion of the rib, the mass was considered to be benign. Its posterior location pointed to a neoplasm of nerve origin rather than a dermoid and because of the typical origin in the uppermost part of the chest, a ganglioneuroma was considered more likely than a neurofibroma, even though a Horner's syndrome was lacking.

Aspiration biopsy was done through a puncture posteriorly. Extremely dense tissue was encountered and only a minute quantity of material could be aspirated. This showed a group of four ganglion cells on microscopic examination, thus establishing the diagnosis of ganglioneuroma.

*Operation* (Dr. Harold Neuhof). The left chest was explored through a long incision and a large, firm, lobulated tumor was exposed apparently originating high in the left

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.



FIG. 1. Ganglioneuroma of the mediastinum



FIG. 2. Ganglioneuroma of the mediastinum, lateral view

paravertebral region where it was firmly fixed, and extending downward and forward occupying a large portion of the left chest. The lung was displaced downward and the heart was displaced mesially. A considerable portion of the tumor extended anterior to the vertebral bodies into the right chest compressing the aorta over which a distinct thrill could be palpated. As the tumor was freed it became evident that its complete removal, if possible, would be attended with great risk because its upper portion was densely adherent and had partly grown into the chest wall between the ribs, thereby making proper exposure for hemostasis impossible. Nevertheless, because the lesion was benign and was already producing pressure effects, it was considered advisable to proceed with its removal. The removal of the growth was effected by dividing it in two portions, thus permitting adequate exposure of its blood supply. Nevertheless, a very small portion, adjacent to the spine at the level of the second intracostal space, was left *in situ* to be removed at a later date. The resected specimens measured 11 x 6 x 4.5 cm. and 6.5 x 4 x 2 cm. in diameter. They were very firm and fleshy and on cut section showed no evidences of degeneration. Microscopic sections were typical of ganglioneuroma.

*Course.* Immediately after the operation the pulses in the arteries in the left upper extremity became palpable, the thrill over the left carotid artery disappeared and the murmur over the heart and the intrascapular region disappeared. However the child developed a typical Horner's syndrome on the left side, undoubtedly due to injury to the sympathetic chain in removing the growth. The child developed a large sterile effusion, but he had a spiking temperature which was found to be due to an infection of the wound. This subsided promptly after drainage.

Ten months later the child was readmitted for resection of the small portion of tumor known to have been left at the previous operation. The only abnormality found at its site, however, was the presence of some dense scar tissue. This was resected and examined histologically, but no evidence of tumor tissue could be found. Apparently the remainder of the tumor, which was very small, had undergone necrosis because of interruption of its blood supply and had subsequently disappeared. Roentgenographic examination 18 months later showed no evidence of recurrence and clinically he was perfectly well with the exception of the Horner's syndrome and a moderate scoliosis of the upper thoracic spine.

Further follow-up, three years after operation, showed no change, no recurrence of the tumor; the patient was symptom-free.

# TRANSITIONAL CELL CARCINOMA OF THE THYMUS IN A CHILD<sup>1</sup>

## FOLLOW-UP REPORT

ARTHUR H. AUFSES, M.D.

[From the Surgical Service of Dr. Harold Neuhof]

In 1934 Dr. A. S. W. Touroff<sup>2</sup> reported a case of transitional cell carcinoma of the thymus in a child. The patient had been given a course of x-ray therapy and had shown marked improvement. At the time of Dr. Touroff's report the patient was in apparent good health. Shortly thereafter, however, the child was readmitted to the hospital because of a recurrence of symptoms, and was operated upon. A tumor was found which could only partially be removed and, in spite of further radiation, the disease progressed, finally ending fatally.

Because of the course of events subsequent to the original publication, it was felt that a follow-up report should be given.

## CASE REPORT

*History* (Adm. 358959). M. K., a female child, aged nine years, was admitted to The Mount Sinai Hospital for the first time on November 2, 1933, complaining of a swelling of the left chest of nine weeks duration. Shortly after birth, the child had paroxysms of coughing, and the diagnosis of an enlarged thymus gland was made. X-ray therapy was given, followed by a cessation of the symptoms at about two months of age. At the age of one year the child had fever without any other symptoms, and a diagnosis of pyelitis was made. Intermittent attacks of fever occurred during the next seven years, each attack being attributed to the same cause. The last temperature elevation occurred in April, 1933. There was no history of tuberculosis in the family, and there were no other relevant diseases. A tonsillectomy had been performed at the age of two and one-half years.

Nine weeks before admission to the hospital a diffuse swelling was noted over the upper anterior part of the left chest. Five weeks later, there was a slight cough, without expectoration. The temperature had been elevated since then. There had been no chest pain, and the swelling apparently had not increased in size. Three thoracenteses were performed at another hospital, and on two occasions bright red blood was obtained; the third aspiration yielded a small amount of brownish fluid. There was a weight loss of five pounds during the two months prior to admission here.

The child appeared well nourished, but slightly apathetic. Physical findings were negative except for the chest; this presented a prominence over the left anterior area. The left shoulder appeared higher than the right, and there was a bulging of the intercostal spaces on the left. By percussion, there was dullness to flatness over the entire left chest. There were distant to absent breath sounds and absent fremitus over the left chest, anteriorly and posteriorly. There was a systolic murmur over the pulmonic area. There was no clubbing of the fingers. X-ray examination showed a large pleural effusion occupying the entire left hemithorax.

Thoracentesis of the left chest on November 3, 1933 yielded a large amount of fluid which on smear showed crenated red blood cells and a few leucocytes. No organisms were present

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

<sup>2</sup> Touroff, A. S. W.: Transitional Cell Carcinoma of the Thymus in a Child. *J. Mount Sinai Hosp.* 1: 17, 1934-5.

on smear or culture. Examination of this fluid for tumor cells showed fragments of transitional cell carcinoma of thymic origin. The fluid obtained on a chest tap on November 7, 1933 produced similar pathologic findings.

Because of the presence of a gonorrheal vaginitis, the child was discharged from the hospital on November 7, 1933 to be cared for in the Out-Patient Department.

From November 15, 1933 to January 10, 1934, she received a course of X-ray therapy totaling 1,200 "r" to the anterior and posterior mediastinums. Examination on July 10, 1934 showed her to be in good general condition, having gained ten pounds in weight. The swelling of the chest had receded. On September 15, 1934, the child was in excellent condition and had no complaints. She was now overweight for her age and height. X-ray examination at this time showed a shadow in the left chest which was smaller than the shadow previously seen; this was interpreted as an encapsulated pleural effusion. The mediastinum was not widened.

*Second admission.* The child was readmitted to the surgical service on November 20, 1934, because of general malaise, a temperature of 104°F., nausea and anorexia of five days duration. Two days before admission, she had pain in the posterior part of the left chest. Her general health had been excellent up to this time. Physical examination showed an increase in retromanubrial dullness, with dullness to flatness over the entire left chest. Breath sounds were of distant bronchial quality, and fremitus was decreased. Laboratory examinations were essentially negative.

On November 26, 1934, bloody fluid was aspirated from the left axilla, and some fragments of tumor tissue which were reported as fragments of transitional cell carcinoma were also obtained. Because of the recurrence of the tumor after what had appeared to be a successful course of x-ray therapy, it was decided that exploratory thoracotomy should be performed.

*Operation.* Thoracotomy and partial removal of an extrapleural tumor was performed by Dr. Harold Neuhoof on December 4, 1934. A scapula mobilizing incision was made and a long section of the fifth rib was removed. A large amount of tumor tissue was immediately encountered. This was curetted and was found to occupy multilocular recesses. A more extensive mass lay anteriorly reaching as far as the parasternal region. Posteriorly, superiorly and inferiorly there were similar but smaller recesses. The tumor appeared to be completely necrotic with the exception of two or three places where more viable looking tissue was noted. The lung tissue or pleura as such could not be identified. After removal of a considerable amount of the tumor, it was evident that complete eradication was impossible. The wound was packed lightly with gauze, and silkworm gut sutures put in place for later closure. It was contemplated to give x-ray therapy through the open wound.

*Surgical pathology* (Dr. S. Otani). Microscopic examination of a fragment of tumor tissue showed a very cellular malignant neoplasm, with scanty stroma and areas of extensive necrosis. The tumor cells were quite large, but showed practically no stroma; their nuclei were round and presented large, distinct nucleoli, and numerous mitoses were seen. All cells were uniform in character; no other structures suggestive of Hassel's body or glandular structures were encountered. Diagnosis: transitional cell carcinoma.

*Course.* On December 10, 1934, x-ray therapy was given through the open wound and continued until January 17, 1935. 1200 "r" was administered during this period.

X-ray examination on January 9, 1935 showed pleural shadows similar to those previously seen. There was no evidence of mediastinal involvement. The patient was discharged on January 9, 1935, to receive dressings and further radiation in the Out-Patient Department.

*Third admission.* On June 24, 1935, the child was again admitted because of cough, dyspnea, elevated temperature and general malaise. From January to June, 1935, she had not been well. A herpes zoster of the left fifth nerve, brachial plexus and intercostals had developed and persisted until admission. The wound had not healed and the disease appeared to be slowly progressive.

*Examination.* The temperature was 102°F. The physical signs in the left chest were similar to those of the previous admission. Hemoglobin was 58 per cent; red blood cells, 3,200,000; white blood cells, 16,550 with 76 per cent polymorphonuclear leucocytes; 21 per cent lymphocytes; 2 per cent eosinophiles, and 1 per cent monocytes. X-ray examination on June 24, 1935 showed an increase in the extent of the shadow in the left chest and, in addition, there were several small nodules in the right lower lobe. These were suggestive of metastases.

*Course.* On July 5, 1935, a palliative course of x-ray therapy was begun but the general condition gradually deteriorated until death occurred on July 16, 1935. Permission for post-mortem examination could not be obtained.

#### SUMMARY

A review and follow-up report of a case of transitional cell carcinoma of the thymus in a child is given.

The original publication was made at a time when apparent recovery after x-ray therapy had occurred.

Subsequently, there was recurrence of symptoms, followed by a partial operative removal, and a subsequent fatal termination.

# NEUROBLASTOMA OF THE MEDIASTINUM<sup>1</sup>

FREDERICK BRIDGE, M.D.

## CASE REPORT

*History in brief* (Adm. 490302). A. G., aged 2½ years, revealed on routine examination a tumor mass on the right posterior aspect of the chest. X-ray examination showed the mass to extend into the posterior mediastinum. There were evidences of separation of the right posterior seventh and eighth ribs, and destruction of the seventh rib. On the basis of the finding of a solitary mass without evidence of metastasis, the diagnosis of ganglioneuroma was made, and it was decided to excise the tumor. It was found to lie between the seventh and eighth ribs; the seventh rib was thinned and excavated. The tumor, of orange size, protruded into the pleural cavity. The pathologic report was neuroblastoma.

*Course.* Two days following operation, paralysis of both lower extremities was noted and a sensory level was found up to the umbilicus. Lumbar puncture revealed no block and no cells in the cerebrospinal fluid. The neurological consultant was of the opinion that the paralysis was due to a vascular lesion secondary to operation, rather than cord compression.

The patient was then referred for the administration of radiotherapy. Six months later it was reported that the paresis had improved considerably, and there were no evidences of metastasis or recurrence.

## DISCUSSION

This case is illustrative of the small but important group of thoracic tumors springing from the sympathetic nervous system.

The sympathetic nervous system takes its origin from primitive cells called sympathogones, in the neural crest. These migrate peripherally to the ganglia and the intramural plexuses of the viscera. The sympathogones give rise on the one hand to the chromaffin cell system, and on the other to the sympathetic ganglion cells. The following schema shows the stages in development:

Pheochromoblast—chromaffin cell

Sympathogones

Sympathoblast—sympathetic ganglion cell

Tumors may originate in cells of each stage of maturation, giving rise to the following groups:

- |   |   |
|---|---|
| 1. Sympathogonioma  | } These are usually classed as neuroblastoma. |
| 2. Sympathoblastoma   |   |
| 3. Ganglioneuroma   |   |
| 4. Paraganglioma (chromaffin cell tumors; pheochromocytoma) |   |

The malignancy of these tumors depends on the degree of immaturity of the cells involved, and the relative proportion of ganglionic and glial elements

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

(gliosis reducing the malignancy). Mixture of cell types often occurs, however, so that one may find ganglioneuromata with metastases, or neuroblastomata in solitary nodules, as in the present case.

The neuroblastomas are found in the suprarenal, the sympathetic chain laterally in the neck, and close to the spine in the thoracic and lumbar regions. The medulla of the adrenal is a special seat of predilection, and the great majority of the described tumors have occurred in this location.

Of 40 neuroblastomas studied by Lewis and Geschickter (2), 33 were found in the adrenal medulla or in the sympathetic ganglia adjacent to it. One-half the cases were under 3 years of age; only five were over 15 years of age. Reid (quoted by Lewis and Geschickter (2)) found that 80 per cent of the cases occurred under the age of  $2\frac{1}{2}$  years. These are highly malignant tumors which

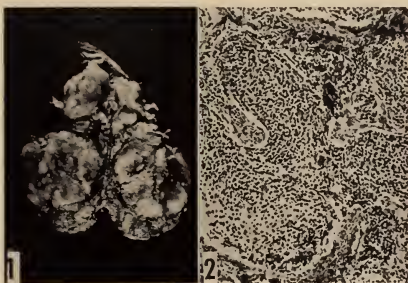


FIG. 1. The main tumor mass is practically round in shape and well encapsulated, measuring  $4 \times 4 \times 3$  cm. Its cut surface is grayish-white with areas of hemorrhage. The tumor appears to be quite cellular. Attached to this tumor mass is a smaller tumor measuring  $2 \times 1.2 \times 1$  cm. which shows an identical picture to that of the main tumor mass except for an absence of hemorrhages on its cut surface. One pole of this tumor is connected with a nerve.

FIG. 2. Microscopically the tumor consists of immature type of neuroblasts; large cell nests are separated by cords of fibrous tissue which contains capillaries as commonly found in neuroblastoma in adrenals. An occasional rosette structure is also encountered. (Pathologic photograph and report by the courtesy of Dr. S. Otani.)

metastasize widely to bones and viscera. There is a marked tendency to hemorrhage. These are the tumors which produce the respective syndromes of Hutchison (with metastases to the skull in left-sided tumors) and of Pepper (with bulky metastases to the liver in right-sided tumors).

As a rule, the neuroblastomas are resistant to radiation, but some cases respond favorably; hence a trial of radiotherapy should always be made. Wollstein (quoted by Scott and Palmer (4)) reported a case living twelve years with radiotherapy. Pertinent to the present case is a report of Wright and Paige (quoted by Scott and Palmer (4)) of a child with cord compression; with radiation the patient has lived six years although the cord symptoms have persisted.

Ganglioneuromata are more likely to present themselves as thoracic tumors; they arise anywhere along the sympathetic chain. Coenan (quoted by Biel-

schowsky (1) claimed that there is a special predilection for the left sympathetic chain. They are usually benign and solitary and are surrounded by a capsule. Rarely they may be multiple and malignant. They may grow to great size; for this reason they may injure organs and blood vessels by pressure and displacement. Therefore it is characteristic of the mediastinal cases that separation and destruction of the ribs are often seen. In some cases they invade blood vessels with the production of blood borne metastases. Of 47 cases collected by Wohl (quoted by Lewis and Geschickter (2)) 29 were under 30 years of age; 29 occurred in the retropleural or retroperitoneal spaces.

Consequently, a thoracic mass present in the posterior mediastinum in relation to the spine should suggest a tumor of the sympathetic nervous system. Sometimes the tumor may extend between the vertebrae into the cord in dumbbell fashion, presenting a thoracic and a spinal cord component. Erosion and separation of ribs and vertebrae are characteristic. In infants neuroblastoma should be suspected, but at any age ganglioneuroma is more likely. Hence removal is justified.

In the present case, the large solitary tumor of the posterior mediastinum separating the ribs suggested the diagnosis of ganglioneuroma; the age, while favoring the diagnosis of neuroblastoma, was not a decisive factor. The favorable clinical progress points to a more benign character of this tumor, or indicates that it is one of those which respond to radiation.

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## METASTATIC CARCINOMA OF THE LUNG<sup>1</sup>

ALFRED L. FLORMAN, M.D.

Primary malignant tumors of the lung in infancy and childhood are extremely rare. Ochsner, (3), in 1937, was able to find in the literature only 24 such instances. However, metastatic tumors of the lung are less rare since many neoplasms found during this period of life invade the blood stream and are seeded in the lungs. The following case report represents such a course of events.

### CASE REPORT

*History.* The patient, aged 4 years, was admitted to The Mount Sinai Hospital with a history of having had an orchidectomy 2 years before because of a mass in the region of the right testicle. On histologic examination this was reported to have been an adenocarcinoma. Following this operation the child was well for over 18 months. Six weeks prior to his admission to this hospital he began to have increasing dyspnea, some cough and fever. An x-ray examination of the chest revealed a mediastinal mass.

*Examination.* On admission the temperature was 101°F., the pulse was 156 and respirations 38 per minute. He was a somewhat undernourished though moderately well developed white child who was obviously acutely ill. He was dyspneic, orthopneic and slightly cyanotic. There was retraction of the lower end of the sternum and the accessory muscles of respiration were being used. There was a brassy cough. There was dullness on percussion over the base of the right lung. Many rhonchi were heard throughout both lung fields and breath sounds were everywhere loud and harsh. Enlarged supraclavicular lymph nodes were felt bilaterally. The spleen was two fingers' breadth below the costal margin. The right testicle was absent. The tonsillar fossae were clean. The fundi were normal.

*Laboratory data.* Hemoglobin, 90 per cent; 18,500 white blood cells with 89 per cent polymorphonuclear leucocytes. X-ray examination of the chest showed a massive enlargement of the intrathoracic lymph nodes and some infiltration at the right base. Aschheim-Zondek test at the time of admission was negative.

*Course.* Because of the cyanosis and marked dyspnea, the child was put into an oxygen tent with some relief. Radiotherapy was started on the third hospital day. The fever persisted between 100°F. and 103°F. for 13 days and then only gradually fell to a lower level. Coincident with the drop in temperature the dyspnea decreased although x-ray film of the chest showed no appreciable change. However, the supraclavicular nodes became distinctly smaller.

About five weeks after admission congestion and edema of the right conjunctiva were observed and on examination the fundus could not be visualized. This was interpreted by the ophthalmologic consultants as being due to separation of the retina. The right eye became progressively worse and soon protruded noticeably. At about the same time the child became more dyspneic and physical signs of consolidation over the entire right lung became more clear cut. The breath sounds also became more wheezing in character and despite oxygen therapy the cyanosis progressed. The child died 7½ weeks after admission.

*Necropsy Finding:* Metastatic lesions from an adenocarcinoma of the right testicle were described in the retroperitoneal, cervical and mediastinal lymph nodes. There was infiltration of this tumor into the trachea and right bronchus. Tumor was found throughout the right lung, over the right parietal pleura, in the left lower lobe and the right orbit.

<sup>1</sup> Presented at the Thoracic Disease Conference, The Mount Sinai Hospital, New York, December 7, 1942.

## COMMENT

MacKenzie and Ratner (2), in 1939, reviewed the subject of metastasis of tumors of the testicle. They pointed out that the average time from onset of symptoms to the demonstration of metastasis is about two years. These are the result of extension via lymphatic and blood streams and are most commonly found in the lungs, liver and kidneys. Obviously the symptoms beyond those of the presence of a testicular mass, depend upon the size and site of the secondary growths. Pain in the testicle is a late symptom.

In 1931, Ferguson and his associates (1) suggested the use of a quantitative Aschheim-Zondek test to aid in the diagnosis and to follow the therapy of testicular tumors. This appeared to be logical inasmuch as most of these tumors are composed of very young totipotent cells which can produce prolan A in large quantities. He observed in a small series of cases that when the tumor responded to radiation, the titre of prolan A fell. Several months ago Dean and his group at Memorial Hospital reported in the *Journal of the American Medical Association* their experience with this procedure. Although in 13 out of 14 of their cases of embryonal adenocarcinoma of the testicle prolan A was present, there was no reliable correlation between hormonal level and clinical course. It is of interest to point out that the Aschheim-Zondek test on the urine of the child whose history has been presented was negative.

The recommended therapy for testicular tumors and their metastasis hinges about the fact that they usually respond at least temporarily to high voltage x-ray therapy. MacKenzie and Ratner (2) reported 3 out of 29 patients so treated to be alive and well after 5 years.

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## THE STORY OF THE MOUNT SINAI HOSPITAL

*The Story of The Mount Sinai Hospital, of which the first nine installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninetyeth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.\**

*The Jews' Hospital in New York was incorporated in 1852 by a group of public-spirited citizens, and in 1855 the doors of its first building on West Twenty-eighth Street were opened to receive patients. Staffed by some of the most prominent physicians of the day, the institution soon proved itself an excellent testing ground for the new methods and techniques which were being introduced into the rapidly broadening practice of medicine and surgery. During the Boyne Day riots, the cholera epidemic, and the Civil War, the Hospital showed its readiness to serve in time of crisis. In 1866 it was given its present name, The Mount Sinai Hospital. By this time it was outgrowing its first home, and in 1872 moved to larger quarters at Lexington Avenue and Sixty-sixth Street, where the expansion in organization paralleled the growth in size and in medical resources. Here, during the next few years the Out-Patient Department was formally established as an independent entity, the Medical Board was organized, the House Staff was enlarged, and the Medical and Surgical Services were separated for the first time. A number of new departments were organized, including New York's first Pediatric Service, under Dr. Abraham Jacobi, and in 1881 The Mount Sinai Training School for Nurses was established. Distinguished surgeons on the Staff and surgery as practiced by them during the early days of the Hospital on Lexington Avenue were sketched.*

### GROWTH AND DEVELOPMENT, 1870-1904

#### X

By the tenth year of its occupancy of the Lexington Avenue building Mount Sinai had already found the facilities that seemed so spacious in 1872 inadequate for the constantly increasing service the Hospital was giving the community. During 1882, 1,692 men, women and children were patients at Mount Sinai as compared with 874 cases cared for in 1872-3. Of those who entered the institution in 1882 all but 76 were treated gratuitously. The Dispensary showed a similar record. In the first twelve months of its official existence, 1875-6, it had held 4,592 consultations and filled 13,004 prescriptions. The number of consultations for 1882 reached 35,785 and 40,025 prescriptions were filled.<sup>75</sup>

This growing activity had already forced the Directors "... to reluctantly

\* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete are welcome and may be addressed to the Historian of the Hospital.

<sup>75</sup> All statistics are from the Annual Reports of the Hospital.

refuse patients for want of room."<sup>76</sup> Therefore, it was with considerable satisfaction that the Board, under the Presidency of Hyman Blum who served in that office from 1879 to 1896, could report that by the end of 1883 a program of rehabilitation and improvement would be completed. Additional wings two stories high were being added to the building. This made possible the setting aside of special wards for eye and ear, and one for gynecological cases. Highly interesting is the fact that when these wards were opened the help of the Training School was immediately enlisted, and its pupils and graduates asked to serve on the nursing staff. The erection of an isolation building for patients who might develop contagious diseases during their stay at Mount Sinai was a marked improvement in facilities. Significant of the type of construction in general use when the Lexington Avenue building was erected is the stipulation in the Directors' plans for "the removal of all woodwork and similar dangerous material." For it had been customary to line the wards and operating rooms with wainscoting and woodwork, absorptive material which was frequently the cause of erysipelas and other infections.

Two years later an additional story was added above the passages leading from the Middle House to the wings. This provided four rooms for the House Staff and ten for private patients for whom there had not been sufficient room before. That such additional space for private patients was needed is indicative of the fact that very slowly the prosperous were accepting the idea of going to a hospital in times of illness. The alterations which were completed in 1885 brought the bed capacity of the Hospital to approximately 200. (Today Mount Sinai provides accommodations for 856 patients.)

There was another problem, however, which could not be solved by this program of building improvements, that of caring for chronic invalids. As early as 1876 the Directors had pointed to the fact that "we have in many cases used the discretionary power given us to receive incurable cases, where we thought we might build up the patient a little for a time, when the condition of the Hospital would admit of their being accepted; but the applications of this class are so numerous that, were we to receive them indiscriminately, the usefulness of the institution would be greatly impaired."<sup>77</sup>

There were no Jewish institutions to receive such cases, and many Jewish patients were disinclined to go to the city hospitals. As a result, there were a few glaring instances where chronic invalids remained in the Hospital practically as permanent charges, one for at least six and a half years.<sup>13</sup> So disturbed were the Directors at this situation and at the inability of the Hospital to cope with it, that in 1880 they adopted a resolution to look into the founding of "a hospital for the gratuitous treatment of chronic diseases" in connection with Mount Sinai.<sup>78</sup> In the following year a proposal to add an additional wing for seventy-five such patients was considered, until it became apparent that there was no room. With the plan obviously impracticable for the Hospital itself, the Board in 1883 resolved to cooperate with the United Hebrew Charities in the organization of

<sup>76</sup> Annual Report of the Directors of The Mount Sinai Hospital, 1883.

<sup>77</sup> Annual Report of the Directors of The Mount Sinai Hospital, 1876.

<sup>78</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, October 17, 1880.

such an institution, with the result that the Montefiore Home for Chronic Invalids was opened in 1884.

The overcrowded condition of the Hospital was somewhat improved by the organization in 1886 of a district service to bring free medical aid and nursing to those applicants whose illnesses could safely be treated at home. The plan had first been discussed by the Board of Directors in 1882, and district nursing had long been an ambition of the Training School. In the first four months the three physicians of the District Corps cared for forty-two patients and made one hundred and fifty visits. The Corps was then enlarged to five physicians, and in the first year of its service presented this record: 412 cases referred by the Admitting Physician to the District Corps; 184 cases cured; 89 cases improved; 139 cases subsequently admitted to the Hospital.<sup>79</sup> As a result medical care was given to 273 patients who otherwise could not have been treated because the Hospital wards were full.

The activity of the Dispensary also in some measure relieved the overcrowding of the Hospital. The Directors reported in 1889 that the Admitting Physician had found it possible to refer to the Dispensary 694 cases not sufficiently serious to be hospitalized.<sup>80</sup> But this in turn demanded expansion—the creation of new departments in the Dispensary and the addition of more members to its Staff. There had already been added an Eye and Ear Department, the Staff of which included Carl Koller. Dr. Koller, now Consulting Ophthalmologist to the Hospital, was famous for the discovery of the use of cocaine as a local anesthetic, which he announced before the German Ophthalmological Congress at Heidelberg in 1884. The news of the discovery spread rapidly through Europe and to the United States.<sup>81</sup> In the late eighties, therefore, the use of cocaine in operations for cataract was in general use at Mount Sinai.<sup>10</sup>

The activities of the Dispensary and the Training School required more adequate quarters than the few rooms in the basement occupied by the one and the private houses which served as a Home for the other. Accordingly, in 1889 the Directors began to plan a building that would house these two divisions of the Hospital. A plot of land was rented on the north side of Sixty-seventh Street, between Lexington and Third Avenues, and construction of the new building began.

Although in 1889 there were still open lots, such as the one leased for the Dispensary and Training School, the neighborhood about Mount Sinai had been built up considerably in the course of the seventeen years since its dedication. Behind the Hospital and facing Third Avenue was the Chapin Home, a Presbyterian Institution for the care of the aged. In 1894 a part of the land between the two institutions, which belonged to the Chapin Home, was made available to the Hospital House Staff for a tennis court.<sup>82</sup> The only means of access was a window in one of the wards and thence to the brick wall which separated Mount

<sup>79</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, June 12, 1887.

<sup>80</sup> Annual Report of the Directors of The Mount Sinai Hospital, 1890.

<sup>81</sup> Wolff, Julius: The Fiftieth Anniversary of the Beginning of Local Anesthesia. *Journal of The Mount Sinai Hospital*, Vol. 1, No. 5, 1934.

<sup>82</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, June 17, 1894.

Sinai from the Chapin Home. This entrance and exit required a bit of athletic accomplishment all its own, especially at the signal that a member of the Attending Staff had arrived, when it was necessary to return with some show of dignity. The signal itself was not exactly conducive to hospital quiet, for the call system of those days was at first a steam whistle located in the yard and later a large gong. The number of ear-splitting blasts or resounding strokes indicated whether the Attending was a member of the Medical or the Surgical Staff.<sup>83</sup>

Beside the public and charitable institutions which had been built along Lexington Avenue, private homes of the prevailing brown stone began to appear in the neighborhood. That the blocks surrounding the Hospital were rather solidly built up by 1889 is merely one detail in a more general expansion. In 1873 the city boundaries had crossed the Harlem River, absorbing Harlem itself and the villages of Morrisania, West Farms, and Kingsbridge. These rural settlements had been swallowed up as the city's northern boundary moved on to Yonkers. "Harlem Village is no more. Harlem as a separate district of the city, easily distinguished, isolated, apart, a refuge from the hubbub of business and traffic, has also ceased to be."<sup>84</sup>

In 1895 Kings, Queens, Richmond, Long Island City, Flushing, and Jamaica were absorbed into Greater New York and the present five boroughs were created.

As New York expanded, means of transportation necessarily improved. Until 1885 the "el" and the horse-car had been the only means of public conveyance. In that year cable-traction cars appeared;<sup>85</sup> but three years later there were still forty lines of horse cars in the city.<sup>86</sup> One of them was the Lexington Avenue "Railroad" which plodded past the Hospital and was not replaced by an electric street car until 1895.<sup>87</sup>

Means of approach to the city were also improving. The year after the Hospital's cornerstone was laid, work started on the Grand Central Terminal for the trains of the Hudson River, New York, and New Haven and Harlem railroads. The structure, on the site of the present Terminal Building, was approached by a trench open to the sky, the same route which today forms the tunnel leading down Park (then Fourth) Avenue.<sup>88</sup> In 1883 the Brooklyn Bridge was finally completed. For sixteen years New Yorkers had seen work proceeding slowly on the mammoth undertaking that was then the longest suspension bridge in the world.<sup>74</sup> The erection of other bridges began ten years after the completion of Brooklyn Bridge; one in 1893, across the Harlem River at Third Avenue; two others in 1895, across the Harlem at 155th Street and at 181st Street; and in 1898, the Williamsburg Bridge.<sup>85</sup>

In the late eighties and early nineties street illumination still depended chiefly on gas. At the Centennial Exposition in 1876 arc lights were exhibited, but their

<sup>83</sup> Notes dictated by Dr. Percy Fridenberg, Feb. 19, 1938.

<sup>84</sup> Van Pelt, Daniel: *Leslie's History of Greater New York*, Arkell Pub. Co., 1898.

<sup>85</sup> Stokes, I. N. Phelps: *The Iconography of Manhattan Island, 1498-1909*. Vol. 3, 1918, privately printed.

<sup>86</sup> *Illustrated New York—the Metropolis of Today*, International Pub. Co., 1888.

<sup>87</sup> Information from New York Omnibus Co.

<sup>88</sup> Information from Offices of the New York Central Railroad.

flickering made them so impractical that they were regarded chiefly as a curiosity. Two years later Thomas Edison presented to the world his invention of the incandescent lamp, and street illumination was one of its first uses.<sup>84</sup> Although in 1888 Broadway was strung with electric lights from Fourteenth to Twenty-sixth Streets, two years later 27,114 gas lights still remained.<sup>85</sup> It is indicative of the skepticism with which electric light was regarded that in 1889, when the Mount Sinai Directors were considering specifications for the new Dispensary building, a motion that it be wired "... for the eventual use of electricity" was defeated.<sup>89</sup> Nor was it ever installed in the Lexington Avenue building which the Hospital occupied until 1904.<sup>86</sup> Gas light illumined the wards, an elaborate gas chandelier hung in the entrance hall, and gas fixtures on adjustable brackets lined the walls of the operating room.<sup>90</sup>

In June of 1890 the Dispensary building was opened. It stood six stories high and was connected with the Hospital by a tunnel under Sixty-seventh Street. The first two floors were devoted to the Dispensary service and were entered by a door on the left side of the building. The four top stories belonged to the Training School and could be reached either by stairs or elevator, through a door at the right. Living quarters for the nurses and rooms for the Ladies' Auxiliary and the Board of Directors of the School made up these four floors. Of Belleville stone up to the first story, with brick and terra cotta above, and its façade elaborately decorated in the style of the nineties, the Dispensary and Training School building still stands today—the home of the Polish Legation.

With this additional space available, the Dispensary could establish the new departments its increased activity demanded. The "Internal" or Medical Department was reorganized into two divisions, one for men, and the other for women. The Eye and Ear Department was separated so that there was one department for diseases of the eye and another for those of the ear, nose, and throat. A new department was created for neurological cases and another for skin and venereal diseases. These, with the Surgical, Gynecological and Children's Departments, formed the nine divisions of the Dispensary's domain. Eleven new appointments were made to its Staff, resulting in a group of twenty-six doctors. Due to the enlarged facilities and a bigger Staff, the Dispensary was able to show a seventy-five per cent increase in its work in 1891 as compared with its record for 1889-90.

The enlargement of the Dispensary Staff was supplemented three years later, in 1893, by additional appointments to the Hospital Staff. These appointments were indicative not only of Mount Sinai's own development, but also of increasing growth and specialization in the medical field as a whole. The study of nervous disorders and of skin diseases were two branches of medicine which had made substantial progress in the closing years of the nineteenth century. Neurology was already a well established field in Europe under such leaders as Carl Westphal and Wilhelm Erb.<sup>58</sup> Although in the United States the subject was less advanced, in the eighties and nineties there were groups of men in Philadelphia,

<sup>89</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, April 28, 1889.

<sup>90</sup> From old photographs of the Hospital.

Boston, and New York who were making notable contributions to neurological literature. Prominent in this New York group was Bernard Sachs, today dean of American neurologists.<sup>91</sup>

Dr. Sachs was appointed Consulting Neurologist to Mount Sinai in 1893. The title of Consulting Neurologist did not then imply, as it does today, that the holder had formerly been a member of the Attending Staff. Because neither the



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Board of Directors nor the Medical Board were sure that there would be sufficient neurological material to warrant the regular attendance of a member of the Staff, a Consulting rather than an Attending was appointed. For three years the Hospital had had a Neurological Department only in its Dispensary, and the creation of this Consultingship marked an increasing interest in the subject.

<sup>91</sup> Report of the Neurological Department of The Mount Sinai Hospital, Dr. Israel Wechsler, 1938.

However no beds were set aside for a special service and neurological cases continued to be sent to the medical wards.

Although he was not a member of the Attending Staff, Dr. Sachs was extremely active in studying the clinical material on the general medical wards. He had been contributing to the field of neurology since 1881, but one of his most important works was completed after he came to Mount Sinai. In 1895 he published *A Treatise on the Nervous Diseases of Children*, the first American publication on this subject.<sup>58</sup> Shortly thereafter he made further important observation on a disease which he named amaurotic family idiocy, a term well chosen by its discoverer with whose name that of Warren Tay is commonly bracketed (Tay-Sachs disease). In 1894 he was elected President of the American Neurological Association, an office to which he was re-elected many years later, in 1932. He was chosen President of the New York Neurological Association in 1896, and twelve years later was again elected to the Presidency. In 1931 he was elected President of the First International Neurological Congress and in 1933 he served as President of the New York Academy of Medicine.

In 1900, seven years after he had been appointed Consulting Neurologist, Dr. Sachs was made Attending to a distinct Neurological Service at Mount Sinai, the first in a New York hospital,<sup>92</sup> with twelve beds set aside solely for neurological cases. Until 1924 he was Neurologist to the Hospital and today, after twenty-four years as a member of the Attending Staff, Dr. Sachs is again Consulting Neurologist to Mount Sinai.

In 1942 Dr. Sachs was honored by his associates, former pupils and a host of friends by a special issue of the *Journal of The Mount Sinai Hospital*, dedicated to him on the occasion of the sixtieth anniversary of his highly fruitful participation in the practice and progress of scientific medicine.

At the same time that a Consultingship in Neurology was created Sigismund Lustgarten was appointed Consulting Dermatologist to the Hospital. Just as neurological work within the Hospital was at first considered experimental, so the specialty of skin diseases, although there had been such a department in the Dispensary since 1890, was hardly thought to require the constant services of an Attending. A student of the great European skin specialists, von Hebra and Kaposi, Dr. Lustgarten was trained not only in his own specialty of dermatology, but also in general medicine, chemistry, and pathology. Coming to the United States from his native Vienna in 1889, he had soon become active in medical circles and quickly gained a reputation as a diagnostician. As a Consultant and later as an Attending Physician to the Hospital, Dr. Lustgarten did not limit his diagnostic work to dermatology alone and frequently was called to attend in the general wards. At that time there were no extensive laboratory tests (until 1893 there had been no Laboratory in the Hospital at all) and diagnosis depended almost entirely on clinical knowledge. The occasion on which Dr. Lustgarten discovered a case of leprosy in the medical wards is famous in hospital annals. Equally dramatic was his diagnosis of mercurial poisoning in a patient who had been isolated for scarlet fever. Like several of his colleagues, Dr. Lustgarten

<sup>92</sup> Interview with Dr. Bernard Sachs, October 10, 1938.

was a man of culture and erudition, a lover of music and a connoisseur of painting, himself a good draftsman and a collector of fine engravings and etchings. Soft-spoken, dignified, a man of great intellectual stature, he commanded universal respect. In 1900 he was made Attending Dermatologist, and a separate Dermatological Service was organized.<sup>93</sup>

In 1893 the Consulting Staff included three other members, in addition to Drs. Sachs and Lustgarten. Dr. Thomas Markoe, the one remaining representative of the Hospital's first Staff, was the only Consulting Surgeon. The two Consulting Physicians were Alfred Loomis and Abraham Jacobi, both of whom had resigned from the Attending Staff ten years before. Upon the death of Dr. Willard Parker in 1884, Dr. Jacobi had been elected President of the Medical Board, a position he still held in 1893. He was now sixty-three, a man of striking and even magisterial appearance. The statuesque head, its gray hair as profuse as ever, suggested "... the living embodiment of some great high priest of knowledge of old."<sup>94</sup> His reputation for integrity as a doctor and as a fighter for improved medical standards had placed him in the leadership of the New York Medical World. As a consultant he was constantly called upon and commanded wide influence.<sup>94</sup> At that time the flow of European immigration was filling the slums on the east side of the city, and sickness among tenement dwellers was a frequent calamity. On such occasions there was an almost pathetic faith in a consultant, "a professor from uptown."<sup>94</sup> Dr. Jacobi was the one most often called in such cases, and the sick poor could not have found a more honest practitioner or one more forgetful of selfish interests. Summoned at the last minute to some emergency case, his entrance was usually dramatic. Dressed in a black overcoat with a flowing black cape, and a broad-brimmed black hat, he would dash up in a black coach drawn by two black horses.<sup>95</sup> He was active in every move of the medical profession. "Nothing of importance associated with the practice of medicine took place unless Jacobi was called on the scene."<sup>94</sup> In 1881 he was elected President of the New York Medical Society, and he was President of the New York Academy of Medicine from 1885 to 1888.

The Attending Staff in 1893 was composed of nine members: five Physicians, one of whom was Attending to the Children's Service, and four Surgeons. Of the Attending Physicians, Dr. Rudisch had been on the Staff for fourteen years and Dr. Heineman for thirteen. Alfred Meyer was a graduate of the House Staff in 1878, and the energetic force behind the establishment of a medical library in 1883. Barnim Scharlau had become Physician to the Children's Service in 1883, when Dr. Jacobi was appointed Consulting Physician. Like Jacobi, he was a practitioner of the old school, who sometimes turned surgeon.<sup>95</sup> The loyalty of this sombre man to Dr. Jacobi was an outstanding characteristic.<sup>15</sup>

The fifth Attending of 1893 was Edward Gamaliel Janeway, "the greatest diagnostician of his day,"<sup>96</sup> a man of lightning movements and perceptions. In

<sup>93</sup> Account of Dr. Lustgarten from an interview with Dr. Richard Hoffmann, May 5, 1939.

<sup>94</sup> Rongy, A. J.: *Half a century of Jewish Medical Activities in New York*, Medical Leaves Inc., 1937.

<sup>95</sup> Biographic Sketch of Edward Gamaliel Janeway, by Emanuel Libman, read before each Janeway Lecture at The Mount Sinai Hospital.

making his examination he would bend quickly over the patient's body, hardly appearing to notice details, yet when he raised his head the diagnosis would be complete, including reasons for the conditions he described. The examination seemed to have taken only two minutes but not an item had been overlooked.<sup>68</sup> There was nothing superficial about this spectacular performance, for Dr. Janeway's knowledge was based on sound clinical experience, an absorbing interest



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in pathology, and brilliant powers of observation. Devoted to his work, he was tireless and enthusiastic, an inspiring leader and talented teacher. His manner was simple, kind, quiet and reserved. Born in New Jersey in 1841, he had graduated from the College of Physicians and Surgeons in 1864 and four years later was appointed Curator of Bellevue Medical College. In 1873 he became Professor of Pathological Anatomy at Bellevue, and later Dean of the School. It was in the wards and the post mortem room at Bellevue that a great part of his extensive clinical and pathological knowledge was gained. Always interested in matters of public health, he served as Health Commissioner of New York from 1875 to 1882. He was a pioneer in the struggle against tuberculosis,<sup>95</sup> and had

pointed out its contagious nature as early as 1882.<sup>58</sup> For many years he was called upon by the city whenever epidemics threatened New York. It is significant that in the training of this great physician, pathology played a fundamental part. The role of science in medicine was assuming an increasingly important position.

The Surgical Staff in 1893 remained unchanged, with Drs. Fluhner, Gerster, Stimson, and Wyeth as its members. Two years later Dr. Stimson joined the Consulting Staff. Of the two special services, Gynecological and Ophthalmological, Drs. Mundé and Gruening continued as chiefs. In this period Dr. Mundé, "king of the Department of Gynecology,"<sup>10</sup> carried on the operative clinics that are remembered as impressive and highly picturesque.

"His (Dr. Mundé's) clinics were attended by many representative visitors and the scene at the beginning of the session was, indeed, striking. The room had been prepared and the space for visitors roped off. The patient was placed on the table in the correct posture. The anesthesia was managed by a member of the House Staff with the barbaric open ether inhaler. At the slightest sign of reaction the ether was pushed almost to the drowning point. Everything in readiness, Mundé stripped to the waist, except for a short sleeved thin undershirt far from concealing his splendid torso, his trousers covered by a rubber apron, entered the arena under the ropes, the veritable picture of a superb prize-fighter."<sup>10</sup>

Of this procedure, Dr. Mundé wrote: "The Surgical Staff endeavor to be scrupulously clean and aseptic at all operations. I myself put on a clean undershirt and a pair of trousers which I keep at the Hospital and which are baked after every operative clinic. I do not believe it possible that more scrupulous antisepsis can be employed anywhere than is done in the operating rooms or wards of The Mount Sinai Hospital. Visitors are admitted to operations with the distinct understanding that they carry no infection with them and refrain from conversation or from handling anyone or anything connected with the operation."<sup>96</sup>

By the nineties, aseptic methods of operating technique had generally replaced the antiseptic, and although instruments were still kept in a carbolic solution, the carbolic spray was no longer used.<sup>71</sup> In the equipment, however, there were glaring violations of aseptic procedure. The usual routine was to don over a previously sterilized long white butcher's coat a rubber apron which could only be washed.<sup>97</sup> The hands were then scrubbed with pure green soap for six or seven minutes by the clock, dipped into potassium permanganate and, to decolorize them, into a strong solution of oxalic acid.<sup>64</sup> By that time they were raw and sore, and frequently there appeared points of irritation which were apt to turn into boils. Some of the Staff used the cotton gloves advocated by von Mikulicz, who himself once operated at Mount Sinai as the guest of Dr. Gerster. It is remembered that he used about twenty pairs of these cotton gloves in the course of a twenty minute operation. Rubber gloves, a tremendous innovation,

<sup>96</sup> Report of the Gynecological Service of The Mount Sinai Hospital from January 1, 1883 to December 31, 1894, Paul F. Mundé, Wm. Wood & Co., 1895.

were introduced into the Hospital by Dr. George E. Brewer who served on the Surgical Staff for one year in 1899,<sup>68</sup> but they were not generally accepted by the Staff, many of whom preferred operating with bare hands. The first gloves reached to the elbow and were therefore somewhat clumsy. Masks were never used by the operator, the interns, or the nurses, when nurses were present. Towels were carefully sterilized and then piled on open shelves where dust promptly contaminated them. The operating room itself, even in the nineties, continued to be lined with unsanitary dark wood and wainscoting. The table used was designed by Dr. Gerster. Made of ordinary wood, it was constructed at an angle and equipped with a trough that led to a pail suspended beneath. The covering was a rubberized material which could only be washed, and was held down to the table by large brass-headed nails.

There were general disadvantages too. In order to protect themselves against carbolic acid solutions, many surgeons wore the *sabots* suggested by Dr. Gerster in his book. The only containers large enough to hold an adequate supply of sterilized bandages were old-fashioned candy jars bought at the corner store and dignified as operating room equipment.<sup>97</sup> Operations were carried on by gas light, as has already been pointed out. There was no head operating room nurse. A member of the House Staff presented the instruments and until 1896 nurses helped only with the dressings. In 1896, however, "Dr. Gerster appeared before the Board and argued in favor of a change in the handling of instruments of the Surgical Department, and the suggestion came out that nurses could receive valuable training and do good service in connection with operations."<sup>98</sup>

One consequence of the gradual adoption of aseptic and antiseptic methods was a slow but steady growth of confidence in surgery, on the part of both patient and surgeon. During the ten years from 1884 to 1894 the annual number of operations increased from 456 to 1311, indicating that surgery was slowly coming into its own.<sup>99</sup> (Today the annual total is approximately eight times the number of operations performed in 1894.) Further indication of this progress is seen in the beginnings of surgical specialization, aside from gynecological and ophthalmological, which had been established early at Mount Sinai. In 1895 a Genito-Urinary Service, commanding ten beds, was organized under Dr. Fluhrer, one of the few such specialists in the United States at that time.<sup>64</sup> But even in the nineties, pre-Listerian surgery was not quite a thing of the past. The story is told of a surgeon who, on coming to the Hospital to operate, was asked if he did not care to wash his hands. "What for?" he replied, "I washed before leaving the office."<sup>68</sup>

In 1893 the Staff was further enlarged by the appointment of assistants to the various services. Nathan E. Brill and Morris Manges were added to the Medical Staff. At first interested in neurology, Dr. Brill had increasingly turned to investigation in internal medicine and did extensive research in blood diseases. In 1910 he described the form of typhus which bears his name, Brill's disease.

<sup>97</sup> Interview with Dr. Martin Ware, April, 1938.

<sup>98</sup> Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, January 12, 1896.

<sup>99</sup> Annual Report of the Directors of The Mount Sinai Hospital, 1895.

Three years later, with Frederick S. Mandlebaum, he was the first to present the clinical features and pathological anatomy of a rare disease described by the French physician, Gaucher.<sup>100</sup> When he died in 1925, Dr. Brill was a member of the Hospital's Consulting Staff. Dr. Manges, later Consulting Physician to the Hospital, became Professor of Clinical Medicine at the New York Polyclinic Medical School in 1898, and in 1911 held the same position at the Bellevue Medical College where he continued to teach for eleven years.

In surgery, Howard Lilienthal and William Van Arsdale were appointed. Dr. Lilienthal, who in 1922 became Consulting Surgeon to the Hospital, was a graduate of the House Staff of 1888. Today he is noted as an authority on thoracic surgery, and the author of a comprehensive and outstanding book on the subject. He is also a past President of the New York Surgical Society, the New York County Medical Society, and the American Society for Thoracic Surgery. Dr. Van Arsdale, a promising young surgeon whose death in 1899 was most untimely, was the inventor of an instrument, the first of its kind, with a saw edge so designed that it could cut a curved line.<sup>68</sup>

Joseph Brettauer, later Consulting Gynecologist to the Hospital, and in 1927 President of the American Gynecological Society, was also appointed in 1893 to the Gynecological Service. "An incisive, bold, sure operator,"<sup>101</sup> he has by his organizing ability and professional integrity left an indelible mark on the Gynecological Service. He was a pioneer in the development of the more extensive type of gynecological operation.<sup>102</sup> In the same year Henry Koplik was made Assistant to the Children's Service. Four years earlier Dr. Koplik had been the founder, at the Good Samaritan Hospital, of the first sterilized milk station in the United States. In 1898 he discovered the spots diagnostic of measles, known as Koplik's sign.<sup>100</sup> When Dr. Koplik died in 1927 he was Consulting Pediatrician to the Hospital to which he had given thirty-four years of distinguished service.

Another addition was Charles May, a graduate of the House Staff of 1884, who was appointed to the Eye Service. Today Consulting Ophthalmologist to Mount Sinai, Dr. May in 1914 devised the method of illumination now universally used in all ophthalmoscopes and known by his name. This method, by the use of convex lenses to concentrate the light, and a solid glass in the shape of a prism, so simplifies the ophthalmoscope that it can be used by any medical man even though he may have no special eye training.<sup>103</sup>

It is significant that in these years the appointments to the Staff, both of Attendings and Assistants, later known as Adjuncts, included many men who had served as interns at the Hospital. Mount Sinai was beginning to assume its place as an educational institution and a creative force in the training of young medical men.

*(To be continued)*

<sup>100</sup> Kagan, S. R.: *Jewish Contributions to Medicine in America*. Medico-Historical Press. 1934.

<sup>101</sup> Report on the Gynecological Service, The Mount Sinai Hospital, Dr. Max Mayer, January. 1939.

<sup>102</sup> Interview with Dr. Harold Neuhof, December 21, 1939.

<sup>103</sup> Information from Dr. Charles May.

## DR. HIRAM N. VINEBERG ANNIVERSARY VOLUME PRESENTATION

*On June 8, 1943 Dr. Hiram N. Vineberg was presented with a special issue of the Journal of The Mount Sinai Hospital dedicated to him by his colleagues, associates and friends.*

*Many prominent men in medicine, former associates and pupils, many close friends and grateful patients came to honor Dr. Vineberg. The meeting was opened by Dr. Isidor C. Rubin, an intimate friend and former associate of Dr. Vineberg. He was followed by others who paid tribute to the sterling character of Dr. Vineberg and to his important contributions in the field of gynecology.*

*The reply of Dr. Vineberg, punctuated by many witty remarks, brought to a close a meeting marked by unusual warmth and sincerity.*

### DR. ISIDOR C. RUBIN:

The Bible has designated three score and ten years to be the allotted span for man on earth in which to thrive and prosper and leave to those who follow him the heritage of a worthy name.

There are those who by virtue of stronger constitutions and prudent lives have had the privilege and the grace of added years. But when some one of us, at the age of eighty-five, is still possessed of every faculty that betokens the vigor and the endowments of a much younger person, surely in the design of things he must have been singled out with a purpose beyond the ken of mere human conjecture, to point a moral as well as adorn a tale. Such a man is Dr. Hiram N. Vineberg, who, at that time in life when one would be expected to be a lonely traveller, finds himself in an auditorium surrounded by friends, colleagues, students and patients, all gathered to do him honor and reverence.

I have known Dr. Vineberg practically all my life. He has been my guide, philosopher and friend throughout my own career, such as it is, and I owe him a debt that can only be measured by those qualities of the human soul that represent, I am sure, in every one who is here this afternoon.

Dr. Vineberg never sought a fame that came with fanfare. At the top of his profession as a great physician, he went his way in the humility that is always an attribute of the great. His sense of humor was the cry of pain of a well-bred man—he took the “buffets and rewards of fortune with equal thanks.”

In a long life, such as Dr. Vineberg has lived, tragedy and comedy frequently meet on the same road. Dr. Vineberg was always the philosopher who looked for the best and found it. He was always and still is a realist. Were I his biographer (and a biographer is a man who walks in another man's dreams), it would take a whole saga to picture his life.

I shall leave it to those who will follow me to tell you of some of the specific highlights in his career. To me, he shall always be the man who held out a torch for my intelligence and a kind word when I most needed it.

MR. LEO ARNSTEIN:

Dr. Vineberg, honored guests and friends of Dr. Vineberg:

I do not know what is accountable for the fact that instead of feting people nowadays at the age of seventy-five, as was formerly the case, we take no notice of them until they reach eighty-five. Whether this is due to the improvement in medical care, to the development of science, to the salubrious air of Mount Sinai Hospital, or to the fact that we live a life of ease while on the Medical Staff, I do not know, but at any rate it has been a great pleasure during the last year or two to have been able to celebrate on several occasions not only the arrival at that age, but the arrival in good health with the ability to enjoy life and the respect and admiration of their friends. Dr. Vineberg is just finishing the fiftieth year of his connection with The Mount Sinai Hospital. Since he joined the staff in 1893 until he was made a member of the Consulting Board, he has been in its active service and has done a wonderful piece of work for the Hospital during that entire time.

Dr. Vineberg, as most of us, started life at a very early age, and he showed his great versatility by first entering trade and earning enough in a short time to see him through college and medical school. Not having a father who could work his way through college for him, he worked his own way through. When he went to McGill University Medical School he was immediately confronted with a problem, and that was that the final examinations were to be held on a Saturday. As he was a Sabbath observer, he could not see his way to taking them on that day, but he interviewed the head of the college and explained why he was not able to take examinations on Saturday, and asked for permission to take them on the following Monday. Permission to do so was granted to him, but with the understanding that the examinations would be somewhat harder in order not to arouse any feeling among the other students, and it was further stated that he would not be eligible for the Holmes Gold Medal, the highest honor the college could confer. He accepted these conditions, but when graduation time came around, he was so far ahead of his fellow students that the Holmes Gold Medal was conferred upon him, in spite of the condition that had been made. I think that is a fair indication of the kind of man Dr. Vineberg was, even in his very early years, and you all know what he was and is in his later years.

I think I have said enough to convey to you, his friends here present, that Mount Sinai Hospital and its Board of Trustees are deeply proud of the fact that Dr. Vineberg has been with us for so many years, that he has served the institution so well, and has added to its luster, and we all look forward to having him with us for many more years, and we shall continue to be proud of him at all times.

DR. BERNARD SACHS:

Dr. Vineberg: It is a great privilege and a greater personal satisfaction to have been asked to write the Introduction to the Anniversary Volume which is

to convey to you the esteem and the affectionate greetings of your many colleagues, friends, former pupils and associates. I am certain I may claim to have known you longer than has any one else in this auditorium, and although our medical activities were in entirely different spheres, I have felt a deep interest at all times in your professional achievements, in the great services you rendered this Hospital and community and above all I honor you for your high (the highest) ethical standards and for your sincere devotion to the welfare of the patients and of the younger physicians working with and under you.

Once I had started out to write a brief introduction, I had the right to delve into your past (remain calm) and to inquire into the beginnings of your career. Through one of your devoted associates, the necessary documents were put at my disposal, and revealed a story which I want this audience to share with me. I thought I was going to bring up something entirely new, but since yesterday some of these facts have been published.

At the very beginning of his career, Dr. Vineberg evinced all the traits of a true gentleman. He always acted in accordance with his principles. Some of his earliest testimonials from his teachers at McGill University and from the laity speak of his high standards and of his unselfish devotion to the interests of those placed under his care. And now for the real story. Quoting liberally from the printed Introduction, I say every one of us must envy him for his early experiences. He may well be proud of his claim that he is a "self made man."

Some think well of themselves because they improve every opportunity offered them. Vineberg created his own opportunities. At fifteen years he left home ("had to dig for myself"), worked hard and at nineteen years had saved enough to enter the Medical School of McGill University, taking the four year course and achieving all sorts of distinction, receiving a gold medal "for highest marks recorded for many years." He began practice in Montreal in 1878, a little ahead of me. For reasons of health and to satisfy a roving spirit, he became a ship's surgeon, visiting Liverpool, London, and finally reaching New Zealand (not by steamer, but on a sailing vessel), now over sixty years ago. The passengers on the Western Monarch in a testimonial dated at Wellington, New Zealand, January 2, 1880, expressed their high esteem of the young doctor as a professional man and a true gentleman. The lady passengers were especially grateful and devoted. That testimonial by the way is a true museum piece worth preserving. Some time later he landed at Honolulu, was appointed by King Kalakaua doctor in charge of a district on the island of Oahu; he was asked to accept a position as Attending Physician of the Leper Settlement on Molokau where he got into touch with the illustrious Father Damien whose great services to that colony Robert Louis Stevenson has made known to the entire world. All this and no doubt much more, Vineberg kept to himself all these years. Drop your modesty, my friend, and during your leisure hours write a full account of those early years. Steal a march on your biographer.

Special acknowledgment is due Dr. Vineberg for his splendid influence on the younger gynecologists. A number of his loyal pupils bear testimony to this. By his rigid adherence to the highest scientific standards, he was recognized

as one of the ablest diagnosticians in his special sphere, and most dependable. He had the courage to admit openly an occasional error and was far removed from a small but conspicuous group of those early, and these later years, who in consultation would "rather appear learned than be right." One of his ablest followers assures me that Vineberg was a great teacher, extraordinarily scrupulous in advising for or against operation, placing the true interests of the patient above all else. Character means more than skill or intellect. No wonder he compelled the admiration of William Osler who was his teacher and a life long friend. All his professors, in special testimonials, speak of him as the "able physician and honorable upright man" or as "the enthusiastic and upright man." We see everywhere emphasis on character. I have known Dr. Vineberg since the year he began practice in New York. From the first meeting I recognized the fine gentleman in speech and bearing. It was not always smooth sailing (it never is); he met some unfriendly criticism with great dignity; he had the will, the conscious urge to succeed. You need not look for any subconscious or infantile motivation.

Friend Vineberg, you have reached the goal of every high-minded physician: the sincere devotion of your patients, sincere friendships among your colleagues; and a reputation for absolute honesty in your relations to your fellow men and fellow workers. Accept this tribute of one who recognizes in you a great physician and above all a genuine American who has added greatly to the dignity of the profession in this beloved country of ours. As I have said to others, "Add to your years, stop counting them." Enjoy the glories of a life well planned and well spent.

#### DR. GEORGE GRAY WARD:<sup>1</sup>

It is a special privilege, as well as a great pleasure, to be invited to pay a tribute of esteem and appreciation to our friend and honored guest, Dr. Hiram N. Vineberg, on this occasion, and I thank your Committee for the opportunity and the honor.

A review of some of the high spots in Dr. Vineberg's career and a survey of his contributions to gynecology and obstetrics will be of real interest to his many friends assembled here, even though you who have worked by his side these many years know his work so well.

He was born in Russia in 1857, and has therefore passed his eighty-fifth year, certainly a long life upon which he can look back with pride in his achievements and on what he has contributed to the advancement of the speciality of gynecology. Indeed as Oliver Wendell Holmes has said,

How blest is he  
Who knows no meaner strife  
Than art's long battle  
With the foes of life.

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<sup>1</sup> Emeritus Chief Surgeon, Woman's Hospital; Past President of the American Gynecological Society.

He graduated in medicine from McGill University in 1878, being honored as the "Holmes Gold Medalist" on that occasion, so that he has lived to witness the evolution of medical and surgical science for 65 years. He has been associated with The Mount Sinai Hospital for more than 50 years, serving as Attending Gynecologist and as Consultant. He is also on the Consulting Staff of a number of other institutions. His interests have been widespread and covered many fields.

He is a Life Fellow of the New York Obstetrical Society and served as President in 1918.

Dr. Vineberg was elected a Fellow of the American Gynecological Society in 1897, was Vice-President in 1926, and was made an Honorary Fellow in 1929. At the time he was admitted a thesis showing original work was required, and he submitted an original vaginal operation for uterine displacement. He was a prolific contributor to the literature, having published some 67 papers on gynecological and obstetrical subjects. To the American Gynecological Society he presented 16 papers on important topics and participated in some 42 discussions.

Dr. Vineberg was especially interested in developing vaginal plastic surgery and in the vaginal approach to abdominal lesions. He was the first in this country to perform and describe Mackenrodt's operation of vaginal fixation for retroversion. He was one of the first here to do the interposition operation for cystocele as devised by Watkins.

He developed an operation to correct retroversion of the uterus by suturing the round ligaments to the anterior vaginal wall via the vagina.

In 1915 he advocated a valuable procedure wherein he amputated the body of a fibroid uterus per vaginam and interposed the stump of the cervix under the bladder as a *pelotte* suturing it to the subpubic fascia to correct a cystocele and procidentia.

For vesicovaginal fistula he devised an ingenious technic of passing traction sutures through the urethra to invert the edges of the fistula and facilitate its suturing.

Dr. Vineberg was much interested in the subject of acute puerperal septic infection and in 1899 showed the courage of his convictions in advocating hysterectomy for its cure in the face of much criticism.

He advocated the ligation of pelvic veins in septic thrombophlebitis, and in 1908 was the first in this country to report such cases; he had operated upon 10 patients with 6 recoveries. He contributed many papers upon this subject.

He wrote much on ectopic gestation taking a position against the deferred operation. He was one of the first clinically to evaluate the importance of chorio-epithelioma malignum and advocated vaginal hysterotomy to explore the uterine cornua to obtain tissue for diagnosis.

His writings covered a wide field and he was most meticulous and thorough in searching the literature so as to make his reports of value. He was an extensive reader of the foreign literature, and he had a generous and liberal spirit with fair-mindedness toward all who worked with him.

Dr. Vineberg belongs to that class of conscientious physicians whose whole in-

terest is devoted to the welfare of their patients and the good of the community. His life work has endeared him to his colleagues and his patients. The relationship which breeds kindness and sympathy in the doctor, and faith, confidence and hope in the patient, is as essential as a scientific knowledge of laboratory tests in the practice of our art.

Dr. Vineberg is an example of what I wish to convey. Throughout his long career he has been not only the wise and able physician, but the sympathetic friend and counselor of his patients.

In closing may I wish him happiness in the words of Pope,

Let joy or ease,  
Let affluence or content,  
And the gay conscience  
Of a life well spent  
Calm every thought,  
Inspire every grace,  
Glow in thy heart  
And smile upon thy face.

HONORABLE DOUGLAS S. COLE:<sup>2</sup>

Mr. Chairman, fellow guests: It is a great pleasure to be here today to honor my good friend Dr. Vineberg and I am happy to have this opportunity of adding my tribute to the many that he has been receiving. Dr. Vineberg is a native of my country and I can claim even closer association with him, as I myself attended McGill University, of which he can make the proud boast of being "one of the oldest living graduates." Further than that, Dr. Vineberg was one of the founders of the McGill Graduates Society of New York, and was President of the Society in 1905-1907, a position that I now happen to occupy.

The many friends and colleagues of the medical profession who have had the privilege of working with Dr. Vineberg will know more than myself of his great achievements in that field. His years have been long and have been filled with outstanding accomplishments. The most significant comment I can make in that connection is that Dr. Vineberg was a personal friend and a valued associate of that other distinguished Canadian who became world-renowned, the great Sir William Osler.

Our guest of honor was born on December 25 more than three-quarters of a century ago. His father was a pioneer of the second group of Jews who settled in Canada in 1855. On his arrival his father with two partners opened a store in the little town of Lancaster, Ontario.

But Dr. Vineberg evidently had a restless spirit or perhaps he was seized with that ambition which led him to such heights in his career. At the youthful age of 14 he left home, penniless, and he made his own way in the world thereafter.

To illustrate his ruggedness of character and the determination of purpose which carried him so successfully through life, I will tell you a story of his early

<sup>2</sup> Senior Canadian Trade Commissioner in the United States; Canadian Consul in New York.

career. I don't believe Dr. Vineberg knows that I have this story, but no doubt he will recall the incidents as I relate them.

In the early days in Canada there were more wholesale and retail houses than there are today—for reasons that are obvious; the large departmental stores have wiped many of them out. One of the largest and most reputable dry goods houses of that time was J. G. McKenzie and Company of Montreal, now long defunct. The manager or head man of this concern was J. P. Cleghorn, a dignified and imposing personality with old-fashioned "mutton chop" whiskers. He was one of the foremost men in Montreal—President of the Board of Trade for three terms; Treasurer of Montreal General Hospital; Director of Molson's Bank, and many other public and financial institutions.

One day Mr. Cleghorn received a visit at his office from two boys who said they had come to buy goods; one was a rugged little fellow about 19 and the other was a mere child who said he was 14, although he looked 12. The young man was the spokesman and in a few words he told his story: that they wanted to start up in business in Foresters Falls which was just bordering on a new and undiscovered rich country; that it was the wealthiest lumbering district in North America, and that it was their plan to penetrate into the depth of that country, supplying the lumbermen and workers with merchandise; this the boy thought undoubtedly would prove a great feeder to the store.

Ordinary politeness and perhaps sympathy prevented Mr. Cleghorn from smiling at the novelty of such a situation. He asked the little fellow, "What capital have you?" The young man answered bravely, "*We have no capital, sir, but we are honest and if you will trust us I feel morally certain that we will repay you and prove good customers.*" Those were the youthful words of Dr. Vineberg!

Mr. Cleghorn was impressed with the very demeanour of the boy, and after consultation with his associates they decided to take a "flyer." I need hardly add their confidence was not misplaced. In time the account ran into thousands of dollars and the firm of H. and H. Vineberg of Foresters Falls, of which Dr. Vineberg was one of the partners, became one of the biggest and most valued customers of the Montreal house.

But I imagine Dr. Vineberg always wanted to study medicine and eventually he made his way to McGill. There he had an outstanding record as a student and when he graduated in 1878 he was awarded the Holmes Gold Medal. This medal was founded by the Medical Faculty in the year 1865 as a memorial to the late Andrew Holmes, one time Dean of the Faculty of Medicine, and is awarded to the student graduating with the highest aggregate number of marks.

That was but the threshold to the long medical career that was to follow and today I salute our distinguished guest, Dr. Hiram Nahum Vineberg, and on behalf of my fellow graduates of McGill University, I pay tribute to our honored guest who has contributed so highly to the traditions of his profession.

MR. ARTHUR HAYS SULZBERGER.<sup>3</sup>

My contribution today springs from a deep sentiment and is, in a way, almost too sentimental—for Mrs. Sulzberger and I are present not solely in our own

<sup>3</sup> President and Publisher of the New York Times (read by Mrs. Sulzberger).

capacity but primarily to represent my parents, Cyrus and Rachel Sulzberger who, with Hiram and Lena Vineberg, made one of those happy quartets founded on mutual respect and affection—a true four-way friendship, because each had something real to offer to the others.

Tender indeed are the memories recalled—the bridge—the talks—the trips together—Yes, even the golf. And though the noted gynecologist occasionally forgot some of his affectionate regard when my father every now and then holed a putt that his perennial opponent had expected him to miss, even causing some non-scientific terms to burst from his otherwise restrained lips—the taste of that particular draught was never too bitter to do other than whet the appetite for the morrow.

And so Mrs. Sulzberger and I welcome the opportunity to be here today. For us, too, the memories are sweet—possibly the more so because they take us back to the days when an older generation carried the ball—when there was someone to turn to who lifted part of the burdens and relieved one of the awful responsibility that now is the lot of our generation.

This is no place to expatiate upon these difficulties. It is, however, a fitting time to suggest how they can be met. I am an incurable optimist and remain convinced that character—individual and national character alone can save us from the endless succession of wars that those gathered here have seen. Give us a *world* of Hiram Vinebergs and we'll not only have bigger and better babies, but we'll put first things first and place the rights of men before the rights of any man. Give us a *nation* of Hiram Vinebergs and we'll have stalwart children eager and willing to take their part in international cooperation. Give us a *group* of peace-lovers as vigilant to keep the peace as doctors are to preserve the health of the community and put down epidemics, and our millenium shall have arrived.

My regret, ladies and gentlemen, is that we have too few Hiram Vinebergs.

Mrs. Sulzberger and I rejoice with you that we have one whom we can honor.

DR. HAROLD NEUHOF:

Your friends, former pupils, and associates who have made the scientific contributions to this volume really are representative of a much larger circle who wish in this manner to pay their respects to your grand career as physician and teacher, and to declare their admiration for your many and varied contributions in your chosen field. In dedicating this volume, as an expression of our deep affection for you we desire as well to dedicate it to Lena Vineberg, your true helpmate throughout your medical career.

DR. HIRAM N. VINEBERG:

Mr. President, Mr. Chairman, Distinguished Speakers, Colleagues, Ladies and Gentlemen, Friends All!

Knowing in advance that I would be eulogized by kind and generous speakers, and not being an impromptu orator, and in fact not any kind of an orator, I took the liberty to write down, and have typed, what I wish to say in response.

In order not to be ungracious, I will admit all that has been said about me, and

even to go a step further, and make the claim that I must have been an excellent and successful teacher. The proof of this claim is the fact that several of the pupils have far surpassed the master. I could name four who are, or should be, in this hall this afternoon, all outstanding in their special fields, and have international reputations.

If I refer to a particular one, it is because he was on my staff during the entire period I was the attending gynecologist in this institution, and it was during then, with the aid of my sponsorship and encouragement, that he was enabled to develop a special form of examination which has opened a new epoch in our specialty, and is known as the "Rubin Test" all over the civilized world.

I would like to say a great deal more about Dr. Rubin as a man and as a devoted and grateful friend, but knowing his modesty I will refrain from doing so.

In speaking of myself I may say I am what may be termed a self-made man. I left home at the age of 14, and from then on battled my own way. Dr. Oliver Wendell Holmes, in his breakfast table series, says he has no objection to self-made men only they are inclined to be too proud of the job.

I confess to having been proud of my job in 1878 when I graduated from McGill University, and was awarded the Holmes Gold Medal, and what made me prouder still was the vociferous applause of my classmates who carried me on their shoulders, singing college songs characteristic of the fine and liberal spirit of the students at McGill University in those days, and I am happy to say that the same spirit still exists, as I learn from my nephew, Mr. Sidney D. Pierce, from Montreal, who had a similar experience many years later.

I ask you all, shouldn't I be intensely proud now of my job, surrounded as I am by a vast host of friends and being made the recipient of so great an honor as has been conferred upon me this afternoon? Well, I can truly say I am. Since this affair was started I have been asked very many questions about myself. The most frequent one has been why did I choose gynecology. My invariable reply has been because I consider women more important and more worthy to be cured and saved than men.

I have no special message to deliver to my colleagues. Medicine has made such an advance during the past decade—the period of my retirement—that they all are better versed than I am. Still a few words from the octogenarian may not be amiss and perhaps will be listened to with patience and indulgence. I would stress that you do not allow yourselves to depend entirely upon the laboratory, the x-ray and the guinea pig, although they are important and are constantly increasing in value. To my mind there is still a good deal to be learned at the bedside, not manners—that is bosh, every gentleman should know that intuitively, but what I mean is taking pains and time to get a full history of the case and not taking anything for granted, no matter how competent the doctor in attendance may be. I could relate some very striking and almost unbelievable examples bearing upon this point, but this is not the place nor have we the time for such a discussion. To the very young man I would say do not over-estimate your knowledge nor your importance.

The following incident may demonstrate what I mean. I was at Atlantic City strolling on the boardwalk, trying to get rid of a bad cold, when a gushing lady

came up to me and said in an earnest tone. "Dr. Vineberg, how can your patients get on without you?" I replied without any hesitation: "I am afraid Madam, they can get along better without me than I can without them." Mrs. Vineberg who was with me was greatly pleased with my answer. You married men know how seldom it is that a wife approves of her husband's repartée.

Before closing, I wish to express my appreciation and gratitude for the cooperation and interest the president has taken in this ceremony.

I wish to say at the same time that from the outset of my connection with The Mount Sinai Hospital, which was as Chief of the Out-Patient Department Gynecological Service, the Lay Board was fair and just toward me, and saw to it that my promotion, in due time, was not hindered by an unfriendly element.

I am deeply indebted to the Chairman and to the Committee and especially to Dr. Joseph H. Globus, the editor of the Journal of The Mount Sinai Hospital, who have given so much of their time and efforts to carry out the difficult task they had undertaken. I thank you all from the bottom of my heart. Let me wish you all a very pleasant and healthful summer.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*The Diagnosis, Incidence, and Significance of Essential Achlorhydria.* A. WINKELSTEIN.  
Am. J. Med. Sc., 203: 419, March 1942.

A combination test including oatmeal gruel, histamine and neutral red was used to diagnose true achlorhydria. "True achlorhydria" signifies a complete and permanent achlorhydria.

Using this procedure it was found that the incidence of true achlorhydria unassociated with the organic diseases usually accompanying true achlorhydria (i.e. essential achlorhydria) is very low (1.2 per cent). True achlorhydria of undetermined etiology is rare. Chronic gastritis is probably the cause of these achlorhydrias.

It is possible that the incidence of pernicious anemia; some of the secondary microcytic anemias; various intestinal disturbances; chronic gall bladder and liver disease; various allergic phenomena; and, above all, gastric carcinoma, may be lessened by the proper study, recognition, and prevention of chronic gastritis.

The possible etiologic factors involved in the chronic gastritis associated with achlorhydria are briefly reviewed and discussed.

*Morbilliform Eruption Following Use of Sulfaguanidine.* R. TURELL AND W. LEIFER.  
J. A. M. A. 118: 977, March 1942.

The authors described an instance of morbilliform eruption following sulfaguanidine therapy. This cutaneous complication did not follow the administration of sulfanilamide, sulfathiazole or sulfadiazine which had been given prior to the institution of sulfaguanidine therapy.

*Absorption of Sulfanilamide from Human Rectum and Colon.* R. TURELL. Internat. Clin. 1: 217, March 1942.

The author states that sulfanilamide administered by rectum in solution or suppository is absorbed. Greater concentration in the blood, indicating better absorption, occurs when solutions are employed. The rectal route is safe and may be utilized whenever the oral route cannot be used. This recommendation is timely because, in hospitals situated in combat zones, the rectal administration of medication is easier and simpler in execution.

*The Effect of a Barbituric Acid Derivative on the Lobeline Circulation Time.* K. BERLINER AND A. LILIENFELD. Am. J. Med. Sc. 203: 349, March 1942.

This experimental study demonstrates the paralyzing effect of a barbiturate on the respiratory center.

Fifty duplicate circulation time tests with a one hour interval were performed. The agent used was alpha lobeline hydrochloride which when injected produces cough. Second in amounts recommended by the manufacturer, 0.18 to 0.27 grams, was administered by mouth immediately after completion of the first test. Prolongation of the lobeline circulation time was observed in the majority of those patients who were actually put to sleep. Remarkable degrees of prolongation, up to 539 per cent, were found among those patients who remained asleep until the insertion of the needle. This prolongation of the lobeline

circulation time after Seconal obviously does not represent slowing of blood flow, but rather an increase in reaction time due to the depressant effect of Seconal on the respiratory center.

The lobeline test should not be employed on patients whose respiratory center is depressed either by drugs (barbiturates, morphine) or by pathologic conditions, especially when Cheyne-Stokes breathing is present. The same applies to the sodium cyanide test or any other method of measuring circulation time which depends on the respiratory center or the carotid sinus.

Ordinary hypnotic doses of a barbiturate may depress the respiratory center to a greater extent than is generally appreciated.

*Proctology in General Office Practice.* R. TURELL. Am. J. Surg. 55: 516, March 1942.

The salient features of the diagnosis and treatment of pruritus ani, hemorrhoids, anal ulcers, anal abscess and fistula, polyps, stricture, anal gonorrhea and anorectal tuberculosis are briefly presented to serve as a guide to those who do not specialize in proctology. Special consideration was given to pediatric proctology, rectal bleeding and ambulatory operative treatment. Established principles and procedures are emphasized and new and important facts, such as chemotherapy for anorectal manifestations of lymphogranuloma venereum and uncomplicated anal gonorrhea, and tattooing of the anal and perianal areas with mercury sulfide for intractable pernicious pruritus ani are discussed.

THE DIAGNOSIS AND TREATMENT OF EPIDEMIC RINGWORM OF THE SCALP<sup>1</sup>

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AND

HOWARD T. BEHRMAN, M.D.

The purpose of this article is to acquaint the practitioner with the pathogenesis and therapy of ringworm of the scalp. At the present time, there is an epidemic of such severity in New York as to constitute a serious menace to the public health of the community.

Ringworm of the scalp is a highly contagious vegetable parasitic disease of children below the age of puberty. For the present epidemic, the sources of infection fall into two main groups for the purpose of classification. The first group, and the less important of the two, is that due to the so-called "animal" type of fungus. In this group, the causative organism is the *Microsporum lanosum*. This organism is usually transmitted to children by infected cats or dogs. Clinically, the disease appears as one or several scaling, inflammatory patches in the scalp (figs. 1 and 2). In this scaly patch, there are found pustules or groups of pustules around the hair follicles as well as broken-off hairs. Similar lesions may be present elsewhere on the body. The hairs can be removed with ease from the infected sites. Microscopic examination of these hairs furnishes a rapid diagnosis as evidenced by the presence of a mosaic sheath of spores around the hair shaft. Further confirmatory aids in establishing a diagnosis include trichophytin tests and cultural studies. Trichophytin is an extract of fungi isolated from patients with ringworm. Due to the inflammatory reaction produced by the "animal" ringworm, immunologic phenomena are elicited as evidenced by a positive trichophytin reaction. Cultural studies on special media (Sabouraud) show dull tan colonies with a lemon yellow substrata within five to seven days. Examination of the infected hairs or scalp by means of Wood's light is corroborative of the diagnosis. This light or filter is composed of glass containing sodium barium silicate and nickel oxide. When placed over a source of ultraviolet radiation, it screens out all wave lengths except those in the near portion of the ultraviolet part of the spectrum (3600 angstroms). These rays impart a fluorescence to hairs infected with tinea, especially those of the microsporum group. The infected hairs appear as short, luminous, yellowish green stubs.

The second group of fungi etiologically responsible for tinea capitis is composed of the so-called "human" type of organism. The present epidemic is composed mainly of cases due to this organism, namely, *Microsporum audouinii*. The disease is spread from one child to another by means of direct contact. It may also be communicated by means of intermediate agents such as incompletely

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sterilized barbers' instruments, combs and brushes, hats, towels and the backs of chairs especially theater seats. The lack of conscious effort on the part of parents of infected children to warn neighbors of the presence of the disease plays an important part in transmission of the infection. The clinical picture of the disease consists of the appearance of one or several small scaling patches on the scalp. These patches are composed of fine scales covered with brittle and broken hair stubs (figs. 3 and 4). The inflammatory reaction is slight and pustulation is infrequently observed. The hairs are not easily extracted due to the ease with which they break following slight trauma. The unfortunate



FIG. 1



FIG. 2

FIG. 1. Large, scaling patch on the scalp of a patient infected with the "animal" type of *tinea capitis*. Inflammatory reaction manifested by perifollicular pustules in lesion and surrounding tissue.

FIG. 2. Lateral view of the same patient

feature of this disease is the fact that the scalp may appear to be entirely normal from a clinical standpoint. In all suspicious or suspected cases, recourse must be had to examination by means of Wood's light. It is amazing to the novice to see an apparently normal and healthy scalp spring into focus as islands of greenish points under the filtered ultraviolet ray. Microscopic examination of the diseased hair is also corroborative of the diagnosis and resembles that seen with *M. lanosum*. The trichophytin reaction is usually negative due to the lack of inflammatory reaction produced by this organism. Cultural studies should be performed in all cases. In about seven to ten days there usually appears a greyish white fluffy culture with a central elevation. The substrata



FIG. 3



FIG. 4

FIG. 3. Several scaling patches on the scalp of a patient infected with the "human" type of tinea capitis. There is no inflammatory reaction present

FIG. 4. Lateral view of the same patient



FIG. 5. Appearance of the scalp three weeks after a roentgen-ray epilation. The patches of depigmentation gradually disappear. They represent the original areas of tinea.

is usually red in color. In the culture mount, the organism may be differentiated from *M. lanosum* by the rarity with which fuseaux (an asexual, oat shaped spore) are found. Cultural mounts of *M. lanosum*, the "animal" type of ringworm, are characterized by the presence of numerous fuseaux.

The distinguishing features of the two organisms are of the utmost importance as regards therapy. *Tinea capitis* of "animal" origin commonly responds to local measures. The reason for this is not due to the fungicidal value of the drugs employed but to the fact that the infected hair is loosely attached to the scalp and therefore easily removed. Accordingly, it is very important to wash the scalp frequently during the period of treatment. Some of the drugs which may be employed are ammoniated mercury (5 to 10 per cent), sulphur (5 to 10 per cent), iodine crystals (5 to 10 per cent) and benzoyl peroxide and quinolor ointment (one-third strength). In resistant infections, which include some cases of "animal" infection and practically all cases of the "human" type, resort must be had to epilation of the scalp by means of roentgen-rays. Attempts to rid the infection by means of manual epilation are usually unsuccessful due to the ease with which the hair shafts break, and to the extent of the disease. The use of thallium acetate salts is mentioned only to be condemned because of its toxicity and potential danger. The sole method available at present consists of epilation of the scalp by means of the roentgen-rays. This treatment necessitates an extremely difficult technique and should be employed only by an expert trained in this field. In brief, the technique consists of the division of the scalp into five equidistant areas to each of which a dosage of 275 to 400 roentgens is applied. Within eighteen to twenty-one days, the defluvium begins and is often complete within a week (fig. 5). At this time, frequent shampoos and applications of mild fungicidal preparations may be employed and should be continued until regrowth of the hair within three months. In the Dermatologic Radiotherapy Clinic, numerous cases of this type ranging in age from two to eleven years have been treated since the onset of the epidemic. In none of these cases were any untoward symptoms or sequelae noted.

#### CONCLUSIONS

An epidemic of ringworm of the scalp is present in New York. The diagnosis and treatment of the various types of this disease are discussed in this paper. The importance of proper diagnosis and therapy in this disorder cannot be over-emphasized because of the urgent need for checking the spread of the disease.

## THE ELECTRICAL ALTERNANS

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The relation of electrical to pulsus alternans has been a controversial subject but in recent years the majority of writers have reached the opinion that the two are produced by the same underlying mechanism (1, 2, 3, 4). While pulsus alternans is not uncommon electrical alternation is unusual (5) and only twenty-two case reports have appeared in the literature (Table I) (5, 7, 8-18, 22).

It is well known that electrical alternans is rarely observed in the presence of pulsus alternans (6) and some authors (5, 9) have even tried to explain the two phenomena by different mechanisms. Another type of alternation, namely, alternating atrio-ventricular and intra-ventricular block, also occurs occasionally but this type will not be discussed in this paper.

Recent observations no longer support the earlier belief that pulsus or electrical alternans precedes death by only days or months (19, 20, 21). Observations of complete recovery following the detection of cardiac alternans have become not infrequent and its occurrence during attacks of paroxysmal tachycardia is not considered of any prognostic significance.

We have observed 16 cases of electrical alternans (Table II) and three of these are being presented in detail because of their unusual interest. In the first case, the electrical alternation was the only objective evidence of myocardial damage due to coronary insufficiency. In the second case coronary insufficiency, occurring postoperatively and presenting characteristic electrocardiographic changes, was accompanied on one occasion by electrical alternans. This disappeared subsequently in spite of rapid deterioration and subsequent death. In the third case either electrical or pulsus alternans was present on different occasions.

*Case 14.* A. B., a 60 year old male was first seen because of a severe anginal attack accompanied by fever and subsequently diagnosed as acute coronary insufficiency. Five serial electrocardiograms taken within the first ten days of his illness showed electrical alternans of the QRS complexes in all four leads as the only abnormality. On one occasion the electrical phenomenon was associated with pulsus alternans. The patient's condition improved and he returned to his previous occupation as storekeeper.

*Case 15* (Adm. 494959). L. H., a 55 year old woman presented an eight month history of nausea, anorexia, vomiting and moderate weight loss. The gastric acidity was found to be normal and roentgen examination revealed a mass in the antrum of the stomach with signs of pyloric obstruction. The hemoglobin was found to be 58 per cent and the blood pressure was 168 systolic and 80 diastolic. Subtotal gastrectomy was performed, the specimen showing a chronic gastric ulcer with foci of adenocarcinoma and submucous metastases. The patient was allowed out of bed on the first postoperative day, and up to the fourth day made a good clinical appearance receiving sulfathiazole for a suspected low grade bronchopneumonia. From the fifth day on she was intensely dyspneic with marked cyanosis and signs of left, right and peripheral failure. Intensive therapy with digitalis, aminophyllin, oxy-

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TABLE I  
Cases from the literature

AUTHOR	CLINICAL DIAGNOSIS	AGE	ELECTROCARDIOGRAM	PULSUS ALTERNANS	CLINICAL COURSE	POST-MORTEM EXAMINATION
Th. Lewis, 1910	1) Paroxysmal aur. tachycardia	?	Alternation of QRS complex	present	improved	—
H. Straub, 1916	2) Lues, arteriose., paroxysm. tachyc.	65	Alternation of QRS complex	absent	improved	—
V. Chini, 1928	3) Essential hypert., angina pectoris	45	Reg. sinus rhythm, alternation of QRS complex	absent	Died within a few days	Marked hypertroph. of left ventricle, marked narrowing of cor. arteries
	4) Arteriosclerosis, aortic stenosis, angina pectoris	?	Sinus bradycardia, alternation of QRS complex	absent	?	—
	5) Arteriosclerosis, nephrosclerosis, myocarditis, aneurys. of aortic arch.	60	Reg. sinus rhythm, alternation of QRS complex	absent	Died one month later	Marked hypertroph. of left ventr., myocardial fibr.
	6) Arteriosclerotic heart disease	?	Reg. sinus rhythm, alternation of QRS complex	absent	?	—
R. J. Levy, 1929	7) Cor. art. disease	42	Sinus tachyc., rate 100, altern. of the QRS complex	absent	Died two weeks later	?
L. Condorelli, 1929	8) Lues, myocarditis, glom.-nephritis	30	Auricular fibrill., alternation of QRS complex	absent	Died under observation	?
	9) Chr. rheum. heart disease, M.S.	50	Auricular flutter, 4:1 response, altern. of the QRS complex	absent	?	—
	10) Chr. rheum. heart disease, M.S., M.I.	48	Auricular fibrill., alternation of QRS complex	absent	?	—
A. M. Master et al., 1931	11) Pneumonia	?	Reg. sinus rhythm, alternation of QRS complex	absent	Died six days later	—
W. Nonnenbruch; J. Rihl, 1933	12) Angina pectoris, heart failure, diabetes	65	Reg. sinus rhythm, concordant altern. of QRS complex. and T waves	absent	improved; died two years later	—
W. Hamburger et al., 1936	13) Essential hypert., cor. art. scler., heart failure	48	Sinus tachyc., 100, concordant altern. of QRS complex. and T waves	absent	improved; died twenty months later	Cor. art. scler., multiple microsc. myoc. infarcts
	14) General. arteriosc., myocardial fibr., heart failure, malignancy	59	Sinus tachyc., 100, alternation of QRS complex	absent	Died eight days later	Multiple minute Ca metast. within myocard. and blood vessels of heart
J. G. Brody et al., 1937	15) Hypertension, congest. hrt. fail.	65	Reg. sinus rhythm, bundle branch block, alternation of QRS complex.	absent	?	—
	16) Chr. rheum. heart dis. M.S., M.I., A.S., A.I., heart failure	39	Reg. sinus rhythm, transient altern. of QRS complex.	present	improved; three years later: marked hrt fail.	—

TABLE I—Continued

AUTHOR	CLINICAL DIAGNOSIS	AGE	ELECTROCARDIOGRAM	PULSUS ALTERNANS	CLINICAL COURSE	POST-MORTEM EXAMINATION
M. Hochrein, 1937	17) Cor. art. disease	58	Reg. sinus rhythm altern. of QRS complex	absent	Died	Complete oocl. of l.a.d.
L. Feldman, 1938	18) Malignancy, metastatic pericarditis	54	Sinus tachyc., 120, alternation of QRS complex	absent	Died nine days later	Metastatic pericarditis, carc. of lung
G. M. Rosario, 1939	19) Myocardial insufficiency	56	Reg. sinus rhythm, left bundle branch block, altern. of QRS complex	absent	Died shortly thereafter	—
	20) Essential hypert., Myoc. insufficiency	?	Reg. sinus rhythm, lft bundle branch block, altern. of QRS complex	absent	?	—
A. Nadrai, 1941	21) Congenital heart disease, situs visc. inversus totalis	9 mos.	Reg. sinus rhythm, no mirror image of ECG, alternation of QRS complex	present	Died	Situs visc. inversus totalis, persist. truncus arteriosus.
J. B. Reisinger, 1942	22) Mediastinal tumor, hemopericardium, coma	45	Reg. sinus rhythm, alternation of the QRS complex. and of QRS compl. and P-waves in subsequent records	absent	Died 25 days after appearance of alternation	Endothelioma of vena cava inferior, perforating into pericardium; hemopericardium 2000 cc.

gen, phlebotomy, etc. resulted only in a transient improvement. The patient died five days after the onset of the acute circulatory episode.

The electrocardiogram taken on the fifth postoperative day showed depression of the RT segments and diphasic T-waves in leads I, II and IV, in other words the characteristic signs of acute coronary insufficiency. These changes became even more pronounced during the following days. Only on the seventh day and not thereafter electrical alternation without sphygmomanometric or pulsus alternans was found. The electrical alternation was well defined in leads I, II and IV, and was found to be concordant between QRS and T-waves.

Post-mortem examination revealed a large pulmonary embolus in the right pulmonary artery.

*Case 16.* R. P., a 41 year old male was seen because of marked exertional dyspnea and mild precordial pain. One and a half years previously an attack of acute coronary occlusion had occurred. Hypertension had been known since that time. Examination revealed considerable enlargement of the heart to the left, the heart sounds were of good quality and a sinus tachycardia from 100 to 140 was present. Over the apex there was heard a presystolic gallop and a short systolic murmur. There were no objective signs of congestive heart failure. The examination of the fundi revealed tortuous, thickened arteries, arteriovenous nicking and organized, flame shaped hemorrhages.

Fluoroscopy of the heart revealed marked enlargement and rounding of the left ventricle. The lower two-thirds of the left cardiac contour showed reversal of pulsation. These findings were regarded as indicative of left ventricular aneurysm.

The electrocardiogram revealed sinus tachycardia rate 140, marked left axis deviation, slurring of the QRS complexes and electrical alternans of the QRS complexes and T-waves in all four leads.

The relationship of the alternating QRS complexes and T-waves was concordant in leads I and IV, and discordant in leads II and III, i.e., in leads I and IV, the smaller QRS

TABLE II  
Authors' Cases

HISTORY, CLINICAL DIAGNOSIS	ELECTROCARDIOGRAM	PULSE	CLINICAL COURSE	POST-MORTEM EXAMINATION
1) A. L., m., 54: Chr. rheum. hrt. dis.: 4 yrs. prior to admission pat. had "rheumatism". Repeated attacks of palpitation since in appr. monthly intervals. For past 6 months attacks 3-4 times daily	Nodal tachycardia, rate 176, alternation of QRS complex in leads I and II	No puls. alternans	Improvement on quinidine therap.	—
2) C. G., m., 23: Chronic appendicitis: pat. was admitted with the diag. of app. abscess which was drained and appendectomy performed. Pat. complained of palpitation postop.	Nodal tachyc., rate 197, altern. of QRS compl. in all 4 leads. Normal after paroxysm	" "	Palpitation lasted for 3 days, did not cause any discomfort. Disappeared spontaneously	—
3) G. W., f., 32: Ulcerative colitis: onset two and half years ago. No cardiac findings. Sudden onset of slight precordial distress and palpitation	Supraventricular tachyc., rate 200, alternation of QRS complex. in all 4 leads. Normal after paroxysm	" "	Carotid sinus and eyeball pressure uneffectful. After adm. of Gm. 1.4 of quinid. paroxysm stopped without recurrence	—
4) S. A., f., 41: Paroxysmal tachycardia, polycythemia vera: since childhood episodes of paroxysmal tachycardia, having become more frequ. and incapacitating. Attacks usually terminated by emesis (ipecac.). Two years prior to adm. a polycythemia vera without circulat. complications was diagnosed	Supraventricular tachyc., rate 216, alternation of QRS complex. in all 4 leads. Normal after paroxysm	" "	Paroxysm present at admission lasted 6 hrs., RSR being restored by emesis caused by 2 drams of syrup of ipecac. No recurrence in hospital	—
5) G. H., m., 5: Paroxysmal tachycardia. No heart disease detectable	Supraventricular tachyc., rate 200, alternation of QRS complex. in all 4 leads. Normal after paroxysm	" "	Paroxysm stopped spontaneously	—
6) H. P., f., 10: Persistent tachycardia of unknown etiology: at the age of two and a half pat. was severely frightened in an automobile accident. One week later a tachycardia of 200 was noted lasting for about 10 years. At the age of 5 pat. went into congest. heart fail. after administr. of quinidine. Full recovery after digitalization with temporary slowing of hrt. rate to 140. 5 years later in spite of persistence of the tachycardia patient was completely well. Endocrine type of obesity was present	Auricular tachycardia, rate 185; alternation of QRS complex. in the standard leads; RT segm. depressed in leads II and III; T waves inverted in leads II and III. At present (age 16) no abnormality	" "	No cardiac abnormality detectable at present	—

TABLE II—Continued

HISTORY, CLINICAL DIAGNOSIS	ELECTROCARDIOGRAM	PULSE	CLINICAL COURSE	POST-MORTEM EXAMINATION
7) G. G., m., 65: Luetic aortitis; aortic insuff.; congest. heart failure: pat. was admitted with fever of 103°F., dyspnea, slight cyanosis, râles at both bases. Marked cardiac enlargement, aortic syst. and diast. m., Corrigan pulse, BP 118/40	Reg. sinus rhythm with occas. ventr. extrasyst.; marked left axis dev.; QRS of high voltage; altern. of QRS compl. in leads I and II; RT slightly depr. in lead I and slightly elevated in lead III; T <sub>1</sub> diphasic	" "	Died 6 days after admission	The heart weighs 600 Gm.; marked hypertr. of left ventr. Lueticaortitis, aort. insuff., general arterioscl., pulm. tbc., miliary tbc.
8) D. M., m., 57: Arterioscl. heart dis., essential hypertension, congest. hrt. failure: History of headaches for 9 years, dyspnea and ankle edema for 1 year. Cardiac enlargement, mod. ascites, ankle edema, syst. murmur over aortic area. BP 218/120	Taken a few days before death: Reg. sinus rhythm, marked left axis dev., QRS of high voltage, alternation of QRS compl. in leads II and III, RT markedly depressed in lead I, elevated in lead III, T waves diphasic in leads I and III (Digit. had been given).	" "	Died a few days later due to congest. hrt. fail.	Not done
9) D. F., m., 75: Arterioscl. heart disease, recent myocardial infarct. essential hypertension, chron. bronchitis and emphysema, bronchopneumonia: pat. was admitted with an acute myocardial infarction. Shortly after admission he developed a bronchopn. and congest. heart failure	First degree heart block, PR measures 0.36 sec. Left bundle branch block: left axis dev., QRS notched and slurred, widened to 0.14 sec, RT slightly depr. in leads I and IV, slightly elevated in lead III, T diphasic in lead I, inverted in lead IV. Alternation of QRS complex, partic. in leads III and IV, and of T <sub>4</sub> concordant to QRS.	" "	Died 9 days after admiss. due to bronchopn. and congest. hrt. failure	Coron. art. scler. with narrowing of right cor. art.; organized, recanalized thrombus of right cor. art. just beyond origin; recent thromb. of right cor. art. just beyond old one; fibrosis and myomalacia with aneurysm dilatation of post. wall of left ventr. Chronic bilateral pneumonitis, mild cyl. bronchiectasis, pul. emphysema and bronchopn. RLL.
10) A. H., m., 51: Arterioscl. hrt. disease, bronchopneumonia: patient admitted with a hist. of cough, hemoptysis, weakness and fever of 5 days duration. Pat. is cyanotic, dyspneic and irrational. Rough syst. murmur over aortic area. BP 130/40. Temp. 103-5°F.	Auricular fibrillation, complete heart block, left axis dev., QRS slurred and notched, RT depressed in leads I and II, T inverted in lead I, diphasic in lead II; altern. of QRS compl. in lead IV, T <sub>4</sub> alternately upright and diphasic concordant with the QRS compl.	" "	Died 7 days after admission in circulatory collapse	Not done

TABLE II—Continued

HISTORY, CLINICAL DIAGNOSIS	ELECTROCARDIOGRAM	PULSE	CLINICAL COURSE	POST-MORTEM EXAMINATION
11) P. L., m., 7: Osteomyelitis of jaw, bacteremia; metastatic suppurative pericarditis: pat. developed septic temp after tooth extraction and tenderness of left jaw; rapid increase of cardiac size due to suppurative pericarditis (staph. aureus)	Sinus tachycardia, rate 160, alternation of the QRS complex. in lead IV, RT segments elevated in leads II and III. These changes were present for two weeks before death with the exception of the alternation which only appeared one day before death	" "	Patient's clinical condition went rapidly downhill. Death shortly after attempted pericardiotomy, 12 days after onset of symptoms	Osteomyelitis of the jaw, suppur. pericard. multiple pul. abscess
12) M. F., f., 15: Chronic rheum. heart disease; patient was admitted in congestive heart failure. Mitral stenosis and insuff. was diagnosed	Sinus tachycardia, rate 158, P waves prominent and notched, QRS of high voltage, alternation of the QRS complex in the standard leads	" "	Patient's condition improved considerably	—
13) A. W., m., 13: Chronic rheum. heart dis., recurrent rheum. fever: first admission for erythema multiforme and chron. rheum. hrt. dis. one year ago. Recurrence of rheum. fever with severe congestive heart fail. Heart markedly enlarged to left and right; right hydrothorax, liver palpable. BP 86/68; Temp. 104°F.	Sinus tachycardia, rate 125, PR-interval measures 0.20 sec. P-waves are notched, alternat. of the QRS complex in the standard leads	" "	Died two weeks after admission in severe congest. hrt. fail.	Acute verruc. endocarditis of the mitral and tricuspid valves; acute pericarditis; passive congestion of all organs, ascites
14) B. A., m., 60: Coronary art. disease, cholelithiasis: patient had an attack of severe precord. pain lasting one hour. Sedimentation rate was increased, temp. rose to 102°F. with a moderate drop of blood pressure. BP during alternation 120/100/70	Sinus bradycardia, rate 55, alternation of the QRS complex. in all leads; otherwise there is no abnormality	Present on one occas.	Uneventful recov., BP several weeks after the acute episode 150/90. His condition could be regarded as improved. Patient has returned to his former occupation as storekeeper. His attack was regarded as being due to acute coronary insufficiency	—
15) L. H., f., 55: Postoperative coronary insufficiency: subtotal gastrectomy for ulcer-carcinoma. Postop. course uneventful up to fifth day; then development of coronary insufficiency, heart failure and periph. col-lapse	Reg. sinus rhythm, left axis dev., RT segments dep. in leads I, II, IV; concordant alternation of the QRS compl. and T-waves in all 4 leads on the 7th postop. day	" "	Died on 11th post-operative day, 4 days after appearance of the alternation	Pulm. embolism in rt. pulm. art.; bronchopn. LLL. Chron. rheum. hrt. disease of the mitral and aortic valve. Left ventr. hypertrophy

TABLE II—*Concluded*

HISTORY, CLINICAL DIAGNOSIS	ELECTROCARDIOGRAM	PULSE	CLINICAL COURSE	POST-MORTEM EXAMINATION
16) R. P., m., 41: Arterioscl. heart disease, left ventr. aneurysm due to previous cor. art. thromb., essential hypertension, congestive failure: myocardial infarction one and a half years ago. Marked dyspnea and congest. fail. since. BP 234/215/148. Fluoroscopy revealed mark. rounding and enlargement of the left ventr. with reversal of pulsation of the lower $\frac{1}{3}$ of left ventr. contour. Alternation could not be detected either by fluoroscopy or by kymography	Sinus tachycardia, rate 140; marked left axis deviation; QRS slurred; alternation of the QRS compl. and T-waves in all four leads, concord. in leads I and IV, discord. in leads II and III. Electrical alternation could not be found in any of the subsequent records	Absent when el. altern. was pres. Present when el. altern. was absent	Patient is alive but completely incapacitated	—

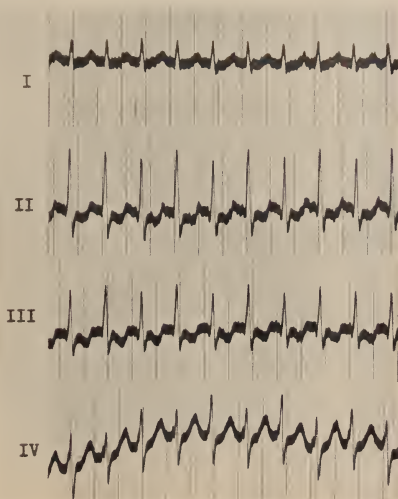


FIG. 1. G. W. F.32 (Case 3 of Table II). Paroxysmal supraventricular tachycardia in a patient with ulcerative colitis. Alternation of the QRS complexes in all four leads. Normal electrocardiogram after cessation of tachycardia.

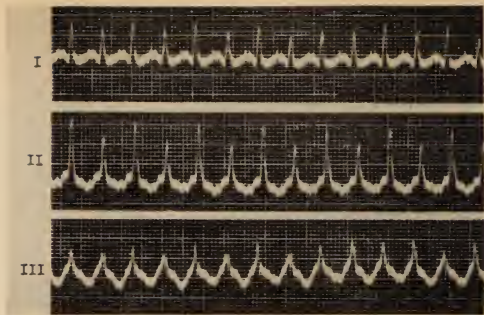


FIG. 2. H.P. F.10 (Case 6 of Table II). Auricular tachycardia in a patient with a persistent tachycardia for about 10 years. Patient was without cardiac signs or symptoms at the time this electrocardiogram was taken. The record shows electrical alternation of the QRS complexes in the three standard leads.

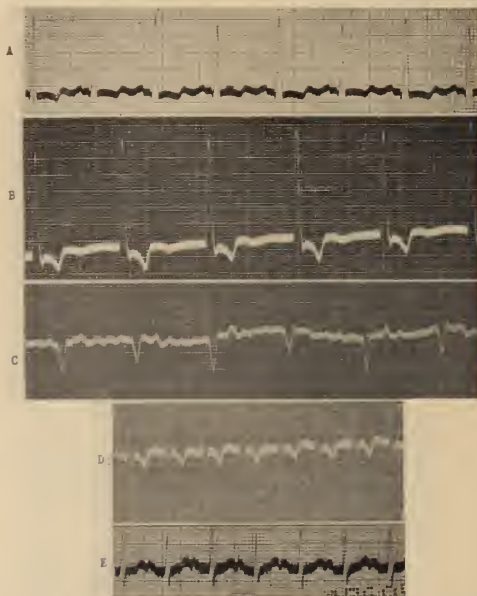


FIG. 3(A) G. G. M.65 (Case 7 of Table II). Electrical alternation of QRS complexes in lead I in the presence of regular sinus rhythm. This was also seen in leads II and III.

(B) D. F. M.75 (Case 9 of Table II). Electrical alternation of QRS complexes and T-waves in lead IV which is illustrated. Lead III showed alternation of the QRS complexes only.

(C) A. H. M.51 (Case 10 of Table II). Concordant alternation of the QRS complexes and T-waves in lead IV in the presence of auricular fibrillation and complete heart block.

(D) P. L. M.7 (Case 11 of Table II). Sinus tachycardia with electrical alternation of the QRS complexes in lead IV only.

(E) A. W. M.11 (Case 13 of Table II). Sinus tachycardia with electrical alternation of the QRS complexes in the three standard leads. Lead I illustrated.

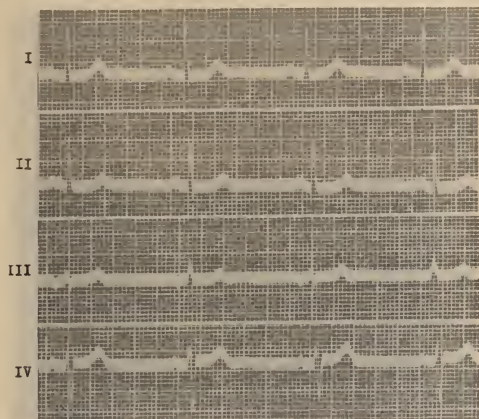


FIG. 4. B. A. M.60 (Case 14 of Table II). Electrical alternation of the QRS complexes in all four leads as the only manifestation of an acute coronary insufficiency.

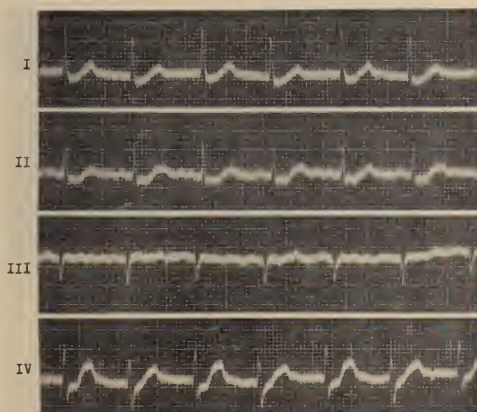


FIG. 5. L. H. F.55 (Case 15 of Table II). RT segments in leads I, II and IV are depressed, indicating acute coronary insufficiency. Concordant electrical alternation of the QRS complexes and T-waves in all four leads.

complexes were followed by semi-inverted, lower T-waves and in leads II and III by upright, correspondingly high T-waves (fig. 1).

No other signs of cardiac alternation could be found at this examination. A second electrocardiogram taken one week later no longer showed alternation in any of the complexes.

Arterial pulse tracing of the right carotid artery revealed distinct alternation, the cardiogram (apical pulse tracing) only an alternation of its auricular components. The phlebogram recorded over the right jugular vein was normal. The phonocardiogram presented discordant alternation, i.e., the smaller beat was accompanied by a first heart

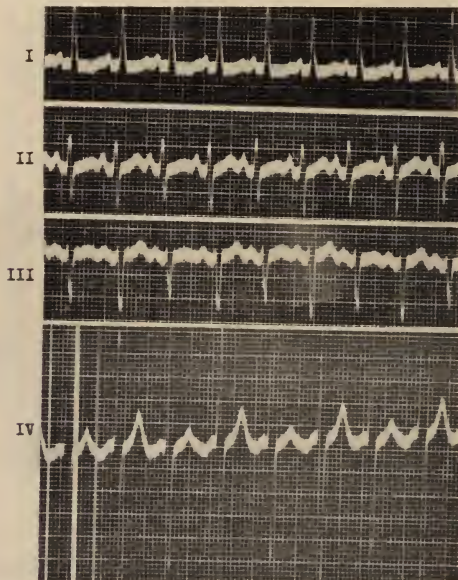


FIG. 6. R. P. M.41 (Case 16 of Table II). Electrical alternation of the QRS complexes and T-waves in all four leads, concordant in leads I and IV, discordant in leads II and III.

sound and presystolic gallop of higher amplitude than the larger beat. There was no alternation of the second heart sound.

In spite of absolute regularity of the electrocardiogram the frequently found irregularity of alternating phenomena in pulse tracings and phonocardiograms could be easily detected. The duration of the stronger beat was 0.5 second and that of the weaker one 0.015 to 0.025 less, both in the arterial pulse tracing and phonocardiogram. The duration of the systole alternated markedly, that of the stronger beat being 0.18 second and that of the weaker one 0.02 to 0.025 less. So actually only the systole alternated, the duration of the diastole being unchanged.

The determination of the blood pressure with the Korotkoff method gave the following

result: At 234 mm. Hg the first sound was audible. From this level down to 218 mm. Hg only every alternate beat came through but thereafter every one could be counted over the cubital artery. Only one diastolic level could be detected at 148 mm. Hg.

There was no alternation of either pulse wave velocity (10.00 m./sec.) or natural frequency of the aorta. The determination of the stroke volume by the physical method of Wezler and Boeger showed that there was a difference of 13 cc. between the stronger and weaker beat (59.8 cc. and 49.8 cc. respectively). The kymogram did not show any alternation in either aortic or ventricular pulsations. Repeated examinations were identical.

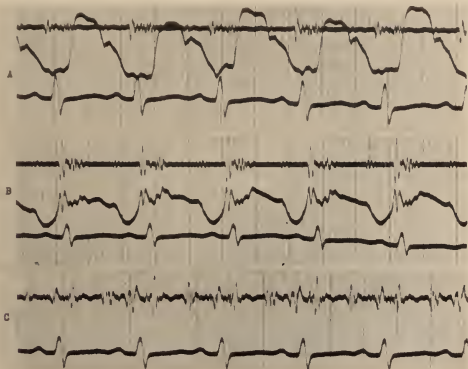


FIG. 7. R. P. M.41 (Case 16 of Table II) cont.

(A) Pulsus alternans in the absence of electrical alternation at a second examination. Discordant alternation of the presystolic gallop.

(B) Alternation of auricular component in cardiogram, concordant with the presystolic gallop and discordant with the pulsus alternans.

(C) Concordant alternation of presystolic gallop and first heart sound, discordant to the pulsus alternans.

#### SUMMARY

The experimental investigation of Hering (1) and Kisch (2), as well as our own observations, indicate that there is no fundamental difference between electrical and pulsus alternans. The underlying mechanism is the same in both (1, 2, 3) namely, a disturbance of the nutrition and metabolism of the myocardium. This may manifest itself as electrical or pulsus alternans or both or may vary from time to time in the same patient.

From a review of the twenty-two cases reported in the literature, as well as of our sixteen cases, it is evident that the mortality rate is high among patients with electrical alternans in the absence of paroxysmal tachycardia. However, we have seen that recovery may occur. The prognosis in each case is best judged not by whether alternation, either electrical or mechanical is present, but by the condition of the heart and circulation as a whole, alternation being but one of many criteria.

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# CAVERNOUS SINUS THROMBOSIS WITH RECOVERY

## CASE REPORT

ARTHUR H. AUFSES, M.D.

*[From the Surgical Service of Dr. Harold Neuho]*

Since the advent of the use of chemotherapy in the treatment of pyogenic infections and septicemia, recovery in a number of cases of cavernous sinus thrombosis has been reported. A review of the literature reveals that several non-fatal cases had been observed in the pre-sulfanilamide era.

The occurrence of cavernous sinus thrombosis has always been so closely linked with a fatal outcome that the survival of the patient tends to cast doubt upon the authenticity of the diagnosis. The classical picture of an infection of the upper lip, nose or forehead, followed by septicemia, proptosis, exophthalmus and death is usually brought to mind. However, it must not be forgotten that the cavernous sinus may be involved from other areas and the disease may run a subacute or even chronic course.

Eagleton, in a monograph on the subject, reviewed the literature up to 1926, and reported twenty-five personal cases, with four recoveries. In three of these the diagnosis was proven by operation. He emphasized the fact that the cavernous sinus could be involved not only from the face but also from the teeth, the sphenoid sinus, the tonsils and the mastoids. He formulated the following criteria necessary for the diagnosis of cavernous sinus thrombosis: 1) known site of infection; 2) septicemia; 3) obstructive symptoms—fullness of retinal veins, proptosis, exophthalmus, collateral venous circulation; 4) ocular nerve paralysis; 5) abscess of the soft parts; 6) meningeal signs. Eagleton also differentiated between the acute infective type of thrombosis and the chronic compensatory lesion. It is in the latter group that most of the recoveries are reported.

Cavenagh, in 1936, reviewed the literature of the previous ten years and found reports of twelve recovered cases; to these he added one of his own. He concluded that up to 1936 there were seven authentic recoveries in the acute infective type and thirty in the chronic compensatory group. Of the seven acute cases, three recovered following operation, and of the thirty chronic cases, two recovered following operation.

Since 1936 a number of recoveries from cavernous sinus thrombosis have been reported. Most of these have been ascribed to the use of chemotherapy, occasionally combined with heparin. One must remember that the thrombosis of the sinus may be due to a non-infected clot which will give all the signs and symptoms necessary for the diagnosis while the actual suppuration is perisinus in location. That this may occur has been shown in excised veins from other parts of the body. In a number of the cases reported as cured by an operation on the cavernous sinus, it is questionable whether the blood clot found in the vein was suppurative in character.

At the present time, we must also evaluate the ability of chemotherapy to sterilize an early infected thrombus, thereby producing an aseptic venous thrombosis. The case reported here presented all the criteria necessary for the diagnosis of cavernous sinus thrombosis: infection on the nose; positive blood culture; obstructed venous circulation; ocular nerve paralysis, and meningeal signs. The staphylococcus antitoxin was given after one blood culture had been reported as negative and clinical improvement had already begun. Its therapeutic effect in this case is therefore questionable.

This patient was one of the early cases of pyogenic sepsis treated by sulfanilamide at The Mount Sinai Hospital. The drug was given in doses of one gram three times daily, which is a small dose even for a thirteen year old girl. Unfortunately, no blood sulfanilamide determinations were made, therefore, we cannot tell how much of a therapeutic effect might be expected from the drug in this instance. Furthermore, it must be remembered that this was an infection due to the staphylococcus aureus upon which sulfanilamide does not have too great an effect.

#### CASE REPORT

*History* (Adm. 414819). M. H., a girl, aged 13, was admitted to The Mount Sinai Hospital, on September 30, 1937. There was nothing of importance in the past, personal or family history. The present illness began four days before admission when the patient's nose began to be painful and gradually became swollen and reddened. The pain increased. On the day of admission the swelling spread to involve the right eye. The patient had a chill, which lasted ten minutes, the night before admission. Pus had been squeezed from the point of maximum swelling, followed by pain over the entire right side of the face, ear, posterior neck and down the back. There was also substernal pain on deep inspiration.

*Examination.* On admission the patient's temperature was 105.6°F. She was lethargic and difficult to arouse. There were occasional facial twitches. The right side of the nose was swollen and tender, with a red  $\frac{1}{2}$  cm. scab in the center. There was spontaneous horizontal nystagmus. There was complete ophthalmoplegia on the right. There was hyporeflexia and a suggestion of right papilledema.

The neurological consultant, on October 1, 1937, found the following: "Right eye bulges more prominently than the left. Patient is stuporous and poorly cooperative. There is slight rigidity of the neck and suggestive Brudzinski sign on the right. The deep reflexes are depressed, abdominal reflexes absent, plantar responses equivocal. There is no gross loss of power in the extremities. There is nystagmus on horizontal gaze, and definite paralysis of the right external rectus muscle. There is good motion of the right eye to the left but very poor response on upward gaze. The right fundus appears to show blurring of the disc margins and increase in caliber of the veins. The left fundus is within normal limits. Localizing signs are suggestive of early cavernous sinus thrombosis but not definitely so."

The following day the neck was moderately rigid; there was a bilateral Kernig and questionable left Babinski sign. The patient seemed more alert but ophthalmoplegia and blurring of the right disc persisted.

Lumbar puncture on October 3 showed an initial pressure of 250 mm. of water, with prompt rise and fall on jugular compression. After removal of 10 cc. of cerebrospinal fluid the pressure was 160 mm. of water. There were 23 cells per cm.; Pandy reaction, negative; no organisms on smear or culture.

The neurological consultant then found the third nerve involvement on the right to be more marked as evidenced by ptosis and increased weakness of upward gaze. Nystagmus

and external rectus palsy persisted. There was suggestive hypalgesia over the right side of the face.

On October 5 the patient was alert and cooperative. There were tenderness and pain in the left wrist suggestive of a metastatic lesion. The neurologist now felt that the picture was definitely that of cavernous sinus thrombosis and the ophthalmologist reported as follows: "There is edema and venous engorgement of the right lids, which apparently was more marked previously. There is no definite proptosis but there is marked limitation of motion of the right eye, externally and upward. There is marked ptosis of the upper lid. There is nystagmus of both eyes on lateral gaze which the patient says has always been present. Pupils react normally. Fundi are normal save for dilatation of the veins on the right.

"Summary. Sixth nerve and partial third nerve involvement, as well as venous stasis presumably occurring behind the sphenoidal fissure in the region of the cavernous sinus."

Marked dilatation of the transverse veins of the right upper eyelid was noted two days later, and on October 9 there was a recession of the edema of the lids but an increase in the congestion of the veins of right upper eyelid. The next day the patient complained of pain and tenderness over the left iliac crest, but in four days the local inflammation had subsided. The eye paralyses were still present. The lesion on the left hand had become asymptomatic and the iliac lesion was much improved. Following this there was gradual improvement until her discharge on November 9, 1937. On discharge there still was a slight ptosis of the upper eyelid and pronounced paralysis of the right external rectus muscle. There were numerous dilated veins over the right upper eyelid.

During her stay in the hospital her temperature ranged between 104.6° and 105.6°F. for the first five days and then gradually subsided. Blood cultures were as follows: September 30, positive for staphylococcus aureus A, 11 colonies per cc.; October 2, 12 colonies per cc.; October 5, negative; October 10, staphylococcus aureus A in two flasks; October 14, negative. The pus from the nasal furuncle yielded staphylococcus aureus A, streptococcus viridans and B proteus. Blood examination on October 5 showed white blood cells, 16,400; polymorphonuclear leucocytes, 79 per cent (non-segmented 25 per cent); lymphocytes, 14 per cent; myelocytes, 4 per cent; myeloblasts, 1 per cent; monocytes, 1 per cent; unclassified cells, 1 per cent; urea nitrogen, 13 mg. per cent; blood sugar, 155 mg. per cent; Wassermann, reaction, negative.

Radiographic examinations of the chest, pelvis, hips and both hands were negative.

*Treatment.* The patient received 100,000 units of Staphylococcus Antitoxin (Lederle), intramuscularly, over a three day period from October 5 to October 7, 1937. Sulfanilimide was given in one gram doses on an average of three times a day from October 1 to October 7 inclusive, totalling 27 gm. orally.

*Follow-up.* The patient was seen in the follow-up clinic periodically after discharge from the Hospital. In December, 1937, there was beginning function in the right external rectus muscle and by April, 1938, the mobility of the eye was normal. There was a persistent slight narrowing of the right palpebral fissure and there was dilatation of the venous network of the right eyelids, more marked in the upper.

In August, 1938, a small lump, which had persisted over the left iliac crest, opened spontaneously with the discharge of a small quantity of pus. The patient was readmitted to the Hospital where a chronic abscess was incised and packed. There was no bone involvement. On May 16, 1939, the iliac abscess had entirely healed and the right eye still showed dilated veins and very slight ptosis.

#### SUMMARY

A case having all the signs and symptoms of cavernous sinus thrombosis is reported. The patient recovered. Both staphylococcus antitoxin and sulfanilamide were used. The antitoxin was given after clinical improvement had

begun; the therapeutic effect of the sulfanilamide is open to question. Approximately seven similar cases of cavernous sinus thrombosis with recovery were reported in the entire pre-chemotherapy era. Approximately the same number have been reported as cured with chemotherapy and heparin.

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## ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

*The continued separation of disease into types can be pressed too far, and a subdivision which may perhaps have some immediate practical use can help to conceal underlying mechanisms held in common and thus to hinder progress in studying disease.—Sir Thomas Lewis*

When chronic disease is closely observed one appreciates that many diseases are not sharply defined genera but transitions of morbid states from one to another. Much of the differentiation that has resulted from more refined observation and more detailed laboratory investigation has tended to confuse rather than to simplify the issue and has caused the classification of disease to be more artificial than biologic. Too often diseases are classified according to a mere grouping of signs and symptoms, rather than in relation to a precise etiology or a well observed consistent pathogenesis. Many chronic diseases, like biologic species, present an evolution from the primitive or embryonic to a full-fledged form. It would be just as consistent to classify the earliest, the intermediate and the final phases of disease as separate entities as it would be to classify the tadpole and the frog as different species.

Most of the confusion in classifying disease comes from an ignorance of the causes of disease. As long as the cause of many chronic maladies is unknown, so long will one be forced to classify disease on the basis of clinical differentials. This does not mean, however, that mere modification of disease processes require separate classification. Time and again conditions that are regarded as separate disease entities eventually prove to be only biologic sports or mutations.

It is not generally realized that those whose entire medical experience centers in hospitals and consultation work see only a small cross section, usually the terminal one of the disease. Of the previous life cycle of the disorder they are ignorant; at best the previous cycle may sometimes be painfully reconstructed. To be able to follow a malady from the beginning to the end is the special privilege of the practitioner and the problem of unraveling the evolution of morbid processes is his. MacKenzie recognized this years ago, and the institute in St. Andrews, in which the very beginnings of disease are studied, is the outcome of his reflections.

In the absence of a knowledge of etiology, one of the best bases for the classification of chronic disease is a uniform and consistent pathogenesis. One may even be unaware of the precise progress of events, of a correct teleologic inter-

<sup>1</sup> This is the first chapter introducing a series of essays by Dr. Eli Moschcowitz in which, as he points out in the preamble, an attempt will be made to interpret certain forms of chronic disease from the biological viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. It is also quite probable that when the publication of the projected series of essays is completed, the several installments will be assembled and printed in a monograph, should the demand for such a volume justify such a step.—Ed.

pretation, but one is safe in saying that maladies that have the same pathogenesis are usually intimately related. At the outset, therefore, diseases may be classified into two great divisions. Those which have a well established pathogenesis possess the dignity of a distinct genus or disease; those which have been classified on the basis of a mere grouping of clinical phenomena are syndromes.

This question of evolution of morbid states is not merely a matter of correct interpretation. Current statistics on nosology lose much of their significance, or even all of it, because the recording clinician did not note in what phase of the process the symptom or sign occurred. One might as well try to correlate a number of unrelated variables.

Studies in this direction will tend not to split up disease complexes, as was so commonly done in the past, but to unify them. In other words, the purpose of these essays is to emphasize the dynamic as opposed to the static approach in the study of disease. Relativity has its field in medicine as well as in physics.

## CHAPTER 1

### THE BIOLOGY OF HYPERTENSION OF THE PULMONARY CIRCUIT

In a series of 770 consecutive autopsies (1) I found arteriosclerosis of the pulmonary artery in 6.5 per cent. Moreover, if simultaneous observations upon the incidence of gross sclerosis of the aorta and pulmonary artery are made, a remarkable circumstance is discovered that appears to have been hitherto overlooked, namely, that they are completely independant. In other words, arteriosclerosis may be present in the pulmonary artery with complete absence in the aorta and vice versa. As a matter of fact, the simultaneous presence of gross arteriosclerosis in both the pulmonary artery and the aorta is the exception rather than the rule. This independence in incidence furnishes, in my opinion, the strongest argument that the mechanistic factor, namely, intravascular pressure, is dominant in the production of arteriosclerosis.

When arteriosclerosis of the pulmonary artery is found, the following underlying conditions are present.

1. Mitral disease, either stenosis or insufficiency. This is by far the most common.

2. In permanent emphysema whether secondary to asthma or to senility.

3. In any lesion of the lungs that causes widespread obliteration of the parenchyma, such as fibroid tuberculosis, bronchiectasis, pulmonary abscess, interstitial pneumonitis (e.g. silicosis), carcinomatous lymphangitis (Greenspan (2)) or widespread pleural adhesions.

4. In cardiac disorders that lead to prolonged right heart failure, for instance, coronary disease, adherent pericardium, "spent" Graves' syndrome or kyphoscoliosis.

5. In open ductus Botalli or other shunts between the right and left hearts, but only when the shunt is from left to right.

Under no other conditions with the rare exception of a decrescent lesion that only occurs in senility, does arteriosclerosis of the pulmonary artery occur.

Arteriosclerosis of the pulmonary artery is independant of age and sex. It

occurs even during the first year of life (Zur Linden (3), Watjen (4)) in the presence of a congenital cardiac lesion. The lesions do not differ from those of arteriosclerosis of the aorta or of the larger trunks of the greater circulation except that atheroma is not so pronounced and calcification is rare. The lesions affect the larger branches and the arterioles simultaneously and are always accompanied by changes in the pulmonary capillaries in the form of dilatation and thickening of the walls (Moschcowitz (1), Parker and Weiss (5)) precisely comparable in morphology to those found in the glomeruli of the kidney in hypertension of the greater circulation. To the summation of these changes, the term, arteriocapillary fibrosis, employed by Gull and Sutton, may be aptly applied.

The common denominator in the conditions above named is an increase in the pulmonary vascular resistance, and while we regrettably have no method of measuring the pressure in the pulmonary artery, we can predicate that on a purely mechanistic basis, the pressure within the pulmonary vascular circuit must be raised. A stenotic mitral valve causes an increased tension within the left auricle which is transmitted backward through the pulmonary veins and thence to the alveolar capillaries. In mitral insufficiency the tension in the left auricle is increased through regurgitation into this cavity. In emphysema, the increased resistance is the result partly of extensive destruction of the capillary bed and partly by compression and stretching of the interalveolar arterioles due to the expansion of the alveoli (Cloetta (6)). Extensive chronic infiltrations of the lung cause an increased peripheral resistance by the destruction of a considerable part of the capillary bed. Failure of the right heart may be direct as the result of mitral disease or indirect after primary failure of the left ventricle. When the left ventricle becomes insufficient, there is an incomplete discharge of blood, as a result the left auricle cannot discharge itself completely, and the blood dams backward through the pulmonary veins resulting in an increased resistance to the flow of blood from the right ventricle. In communications between the two sides of the heart (when the shunt is from left to right) the increased resistance is due to the increased quantity of blood thrown into the right heart through the open communication. The explanation for the increased resistance in the pulmonary circuit following advanced kyphoscoliosis is not entirely clear. It is partly due to compression of the lungs by atelectasis and compensatory emphysema, to kinking of the pulmonary vessels, and to the attacks of repeated bronchitis to which these patients are subject. (Fishberg (7)).

These mechanisms fulfill the requirements of Wiggers (8) for the production of hypertension of the pulmonary circuit, namely, 1) the minute output of the right ventricle, 2) the resistance and capacity changes in the pulmonary circuit, 3) back pressure resistance produced in the left heart by changes in the systemic circuit.

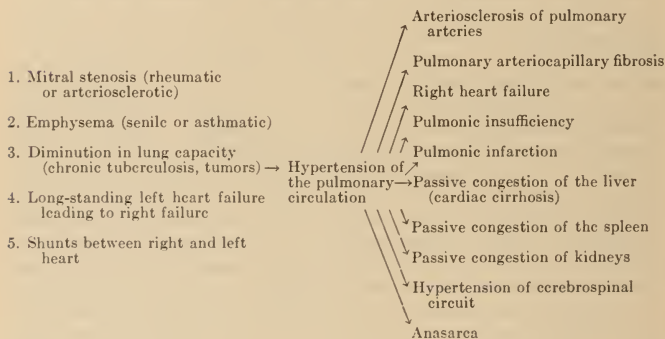
Whether there is a primary sclerosis of the pulmonary artery is very much open to question. I (9) have already discussed the matter in the past. The number of reported cases are few, and when sufficient data are at hand, by

far the majority of reported cases do not pass a strict critique. This applies especially to the much quoted cases of Ayerza's disease, which on strict analysis deserves no recognition for it is in no sense a primary arteriosclerosis but is a condition secondary to various pulmonary lesions. Moreover, there is no proof that it is sphilitic.

*The clinical evolution of hypertension of the pulmonary circuit*

The first consequence of clinical importance is anoxemia due to the interference of the passage of oxygen because of the increased thickness and fibrosis of the capillaries of the alveolar wall. In shunts between the right and left hearts the anoxia is aggravated by the amount of unsaturated blood that is poured into the left heart. The anoxemia results in an increase in the percentage of reduced hemoglobin in the blood resulting in one of the conspicuous clinical

EVOLUTION OF HYPERTENSION OF THE PULMONARY CIRCUIT



phenomena of hypertension of the pulmonary circuit, namely, cyanosis. Lunds-gaard and Van Slyke (10) have estimated that it requires at least 6. to 7 per cent mean capillary unsaturation of oxygen before cyanosis appears. When failure of the right heart ensues, the cyanosis is enhanced because of two super-imposed mechanisms: the slowing of the peripheral capillary flow resulting in increased reduction and the increase in venous pressure. Goldschmidt and Light (11) have shown that cyanosis is in large part due to the subcapillary venous plexuses, even in the absence of capillary unsaturation.

The first compensatory result of the prolonged anoxemia is polycythemia, produced by a hyperplasia of the bone marrow.

The succeeding compensating mechanism is an increase in circulating blood volume. This is observable only in long standing cases of hypertension of the pulmonary circuit, especially those that have been through repeated attacks of failure. The mechanism is allied to the polyuria that follows progressive

renal insufficiency. For a long time, especially among hematologists, secondary polycythemia was differentiated from polycythemia vera by the fact that in the latter the blood volume was uniformly high while in secondary polycythemia it was uniformly low; but the transition in secondary polycythemia from a low to an elevated blood volume is altogether too common to be employed as a differential.

Parallel with the foregoing, other compensatory mechanisms following hypertension of the pulmonary circuit take place. First, progressive hypertrophy and eventually dilatation of the right ventricle. Second, dilatation of the pulmonary artery with the development of a pulmonary conus visible by x-ray. In long standing cases, the resulting dilatation of the pulmonic ring results in pulmonary artery insufficiency and the development of a Graham-Steele murmur. Occasionally, the dilatation of the main branches of the pulmonary artery may be so great as to produce dancing shadows at the hilum of the lung. This is particularly notable in cases of so-called primary dilatation of the pulmonary artery (Oppenheimer (12)). Third, concomitant with the sclerosis of the pulmonary artery there occurs sclerosis of the lining of those chambers of the heart that are subject to increased pressure. These are usually the left and right auricle and the right ventricle. In uncomplicated emphysema when the peripheral resistance is within the capillary bed, the left auricle is not involved. The pulmonary veins also, as a rule, become involved by phlebosclerosis, except of course in emphysema. In my observations, sclerosis of the lining of the left ventricle does not occur in hypertension of the pulmonary circuit except when the latter is secondary to some lesion that produces primary failure in the left ventricle, such as an aortic lesion, coronary sclerosis or hypertension of the greater circulation.

Eventually, in protracted cases of hypertension of the pulmonary circuit when the dilatation of the right ventricle becomes extreme, dilatation of the tricuspid ring ensues, resulting in a relative tricuspid insufficiency. Such an insufficiency is further enhanced by sclerosis and thickening of the valves, that goes hand in hand with the sclerosis and thickening of the endocardium.

Further anatomical consequences of hypertension of the pulmonary circuit are congestion of the viscera, especially of the lungs, liver, spleen and kidneys. These lesions are due primarily to venous engorgement but not necessarily, it should be emphasized, to an increased venous pressure. These morphologic changes do not as a rule affect the function of these organs in the compensated phase of hypertension of the pulmonary circuit.

In time, unless life is compromised by intercurrent disease, failure ensues due to the breaking down of the compensatory mechanisms. A circulatory balance is maintained for a long time because the right side of the heart compensates for the increased resistance by an increase in the amplitude of the contraction of the ventricle. But the initial tension, if continued, eventually stretches the ventricular walls beyond the point where a complete contraction is possible, and a certain amount of residual blood remains in diastole within the right ventricle, resulting in dilatation. This dilatation in turn forces the right auricle

to empty against a positive pressure and an increase in venous pressure results. A rise in venous pressure therefore is one of the earliest manifestations of right-sided cardiac failure and the degree of the elevation corresponds broadly to the degree of failure. Usually, right sided heart failure responds to therapy, but recurrences are the rule and in time the attacks become progressively less responsive, become more frequent and a time comes when a state of chronic failure persists. When this arises, a host of secondary and widespread physiological and morphological changes occur which are reflected clinically. These may be discussed topographically.

a. *Lungs.* The later stages of arteriocapillary fibrosis become manifest. The alveolar walls become greatly thickened with corresponding diminution in the size of the alveoli with resultant diminution in vital capacity. The fibrosis progressively increases and in exceptional instances, reversion to the embryonal type of lung takes place. As the result of a combination of the slowing of the blood stream, pulmonary engorgement and arteriosclerotic disease of the blood vessels, hemorrhagic infarcts are common which may remain as such or induce consolidation in greater or lesser areas. In the process of healing, infarcts may increase the fibrosis. These morphological changes result in an increasing anoxemia, cyanosis and polycythemia.

The dyspnea which in the compensated phases was exertional is now orthopneic. Hemoptyses are common and occasionally pneumonic consolidation ensues with its consequences.

b. *Pleura.* The cause for the development of hydrothorax in right-sided heart failure is in a large measure the resultant of the localized expression of general venous engorgement. But there must be other factors to account for its frequent unilaterality and especially for its common localization to the right side. A complete answer to this problem has not yet been adduced. For a discussion see (Fishberg (7)).

c. *Liver.* In chronic failure, the venous engorgement of the liver causes an increase in size. In my experience, enlargement of the liver sufficient to make it palpable does not as a rule occur in hypertension of the pulmonary circuit unless failure is or has been present, and the longer the history of failure, the larger the liver. The morphologic changes that take place in the liver in prolonged right sided cardiac failure are particularly pertinent in respect to the development of cardiac cirrhosis. The conventional explanation hitherto has been that cardiac cirrhosis is the result of a replacement fibrosis consequent to the atrophy pressure of the liver lobules that occurs around the dilated central veins. Some years ago (13) I submitted another explanation based upon the finding of phlebosclerosis of the hepatic veins. Such a sclerosis is only found in long standing cases of hypertension of the pulmonary circuit with a history of repeated attacks of failure. The only reasonable explanation for this phlebosclerosis is the prolonged elevated venous pressure within the hepatic veins transmitted backward from the inferior vena cava into the hepatic veins. Indeed, I pointed out at that time that increased venous pressure is the *sine qua non* for every variety of true phlebosclerosis found in the human organism. In my

interpretation, cardiac cirrhosis represents a capillary sclerosis due to the further transmission of the increased pressure in the hepatic veins directly into the communicating central veins. In other words, the mechanism is precisely analogous to the conditions encountered in the pulmonary circuit. In the liver the hepatic veins occupy the place of the pulmonary artery, while the capillaries around the central veins represent the capillaries of the pulmonary alveoli. The main differences between the two systems is that in one the main vessel is arterial while in the other it is venous and while in the former the blood flows away from the heart, in the liver it flows toward the heart; but these differences do not minimize the significance of the pressure changes. It remains a fact that cardiac cirrhosis of any degree at least, is never found unassociated with sclerosis of the hepatic veins, and in patients in whom a prolonged increase in venous pressure can be predicated. Some of the most pronounced instances of cardiac cirrhosis I have ever encountered occur in patients with constrictive pericarditis, in whom prolonged high venous pressures are the rule.

In the early stages of hypertension of the pulmonary circuit the engorged liver represents a compensatory phenomenon and serves as an important component of the various venous blood depots that act as a release for the increase in venous pressure. In the later stages, when cirrhosis has supervened this blood depot becomes considerably compromised and renders compensation more difficult to attain. Furthermore, as a result of the increased resistance engendered by the sclerosis of the intrahepatic capillary barrier, an increased pressure in the portal circuit ensues, and if sufficiently intense, ascites results.

Concomitantly with these changes, other functions of the liver become compromised. Thus with the bromsulfalein test, Jolliffe (14) found impairment of liver function in 90 per cent of his cardiac patients. The urobilinogen is usually increased in the stools and in the urine (Eppinger). Hyperbilirubinemia is the rule in advanced right-sided failure and in a broad way parallels the duration and the intensity of the failure. If sufficiently pronounced it produces jaundice.

*d. Spleen.* In the early stages of hypertension of the pulmonary circuit without failure, the organ is deeply congested and cyanotic; the venous sinuses are dilated and engorged with blood and while the organ is enlarged it is rarely palpable. When failure takes place, the organ enlarges considerably, but at the same time, fibrosis occurs of varying degrees depending upon the duration of the failure. The subsequent contraction neutralizes whatever enlargement the congestion may entail, which, in all likelihood, explains why palpable spleens in congestive heart failure do not occur as often as one would expect. Indeed, in long standing cases, the spleen may shrink to less than normal size (cyanotic atrophy.) When the spleen becomes palpable in congestive failure, cardiac cirrhosis is as a rule prominent. The cause of the splenic sclerosis is not clear, but in view of the pathogenesis of cardiac cirrhosis which we have submitted, the likelihood is strong that a similar mechanism holds in splenic sclerosis, namely an increase in the venous and capillary pressures.

*e. The kidneys.* It seems remarkable that even in prolonged right-sided

failure from uncomplicated hypertension of the pulmonary circuit, the morphology of the organ is so little unaffected. It is true that a slight increase in the intertubular connective tissue results but never in sufficient amount to produce any considerable degree of contraction. Obviously when right-sided failure is consequent to a previous left failure, the result of hypertension, more profound changes are found in this organ but these are consequent to the hypertension of the greater circulation. In pure hypertension of the pulmonary circuit, the function of the kidney is not affected, but when failure sets in, various manifestations of disordered renal function become manifest. The first evidence is oliguria accompanied by a high specific gravity of the urine. Whether the oliguria is the result of slowing of the blood flow, increased capillary pressure or venous congestion has never been precisely determined. In a considerable measure, oliguria is due to extrarenal factors, meaning thereby that fluid is shunted away from the kidney by development of edema. Proteinuria, even of considerable degree, is present in most cases of right-sided heart failure due, no doubt, to the increased permeability of the glomerular capillaries. Casts are usually present. Azotemia is by no means uncommon, especially in prolonged and advanced degrees of right-sided failure, and is always associated with marked oliguria. Likewise the excretion of phenolsulphonthalein is often diminished due again to the oliguria. As a rule, all these evidences of impaired renal function subside more or less promptly if compensation can be restored, but in advanced cases, one or more of them may persist.

*f. The central nervous system.* Strangely enough, little is known of the anatomical changes in the brain in uncomplicated right-sided heart failure following hypertension of the pulmonary circuit. Obviously there is venous congestion. Edema is usually slight or completely absent, even in the presence of marked peripheral edema. The explanation for this relative freedom from edema is baffling. The congestion or edema or both, when present, may cause an increase in the size of the brain. But marked anatomical changes in the cerebrospinal system are conspicuously absent. Without doubt, therefore, many of the symptoms of cerebral disorder in primary right-sided failure are the result of disturbances in function. I believe with Fishberg (7) that the psychoses so frequently observed in the terminal stages are largely the result of excessive dehydration.

The cerebrospinal fluid pressure in primary right heart failure is often elevated, due to the increase in pressure within the cerebrospinal veins. This was demonstrated by Friedfeld and Fishberg (16) in right-sided failure and by Kessler, Moschcowitz and Savitzky (17) in secondary right-sided failure following hypertension of the greater circulation.

*g. Subcutaneous tissues.* Peripheral edema is one of the prominent evidences of right sided failure. In the early phases, the edema is latent and indirectly proportionate to the diuresis obtained by therapy. There is abundant evidence that, in the largest part at least, the edema is due to the increased hydrostatic pressure in the venous end of the capillaries which overcomes the neutralizing effect of colloidal osmotic pressure of the plasma. When the edema is of long

standing, a hypoproteinemia results due to the loss of protein that has escaped into the subcutaneous tissues, contributing to the already existing peripheral edema. A further reduction of the blood protein may occur as the result of a persistent and considerable proteinuria or an inadequate protein intake, or frequent tapping of pleural or abdominal exudates. Increased permeability of the capillaries may be a factor in the production of subcutaneous edema, because as Landis (18) has shown, anoxemia of even short duration renders the capillary more permeable to protein. However, as Fishberg (7) argues, permeability of the capillaries cannot be a factor of significant importance because the protein content of the edematous fluid in right heart failure is low.

The capillaries at the base of the finger nail, viewed by the Lombard-Mueller method are considerably dilated in hypertension of the pulmonary circuit. The dilatation is aggravated when failure arises.

*h. The left heart.* While failure following hypertension of the pulmonary circuit is more frequent following left-sided failure than the primary type, left-sided heart failure following right is, in my experience, exceedingly rare as a pure form. Usually both right and left-sided heart failure are associated. There are two possible explanations for the effect upon the left ventricle by failure of the right: 1) A sustained and progressive rise of effective venous pressure must eventually influence the work of the left ventricle. According to Starling and his co-workers (19), the left ventricular muscle increases its stroke volume. This inevitably leads to hypertrophy and eventually to dilatation. An increased left ventricular discharge is necessarily followed by an increased discharge of the right ventricle so that a vicious circle is established that takes its toll upon both sides of the heart. 2) The anoxemia must augment the work of the left ventricular muscle that is already overburdened by an increased venous return. Such a heart requires more oxygen than normal but the amount falls short owing to reduction in coronary flow that accompanies dilatation and hypertrophy of the left ventricle. (Hyde (20), Marowitz and Lahn (21)). In this way, another vicious circle is set in motion.

Disturbances in function of other organs, for instance, the *pancreas*, *adrenals* or the *ductless glands* are not detectable with present methods.

This discussion of the effects upon the organism of primary hypertension of the pulmonary circuit, both compensated and decompensated, cannot be concluded without a word or two upon the effect on the basal metabolic rate. That the basal metabolic rate is normal in the compensated phases of cardiac failure and elevated in the decompensated phases is a well attested clinical observation. The increased oxygen consumption is due, in large part at least, according to DuBois (22) to the dyspnea and the increased work of the respiratory muscles. In edematous patients with little or no dyspnea, I have found that the basal metabolism is sometimes low, reaching sometimes minus 30 per cent. The explanation for this curious phenomenon, as was pointed out some years ago (23) is the fact that the edema acts as a "suit of clothes" preventing the dissipation of heat.

It is necessary to emphasize that it is not the sclerosis of the pulmonary

arteries that is responsible for the clinical evolution, but the hypertension of the pulmonary artery that has produced this sclerosis. In other words, the sclerosis is the result and not the cause. Primary sclerosis of the pulmonary artery, as I have pointed out already, is rare, if it exists at all. The only manner whereby the sclerosis can contribute to the clinical picture is the predisposition to thrombosis and infarction.

Furthermore, hypertension of the pulmonary circuit and right-sided failure must not be confused, no more than hypertension of the greater circulation and left-sided heart failure. Failure is sequential to the hypertension.

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## THE STORY OF THE MOUNT SINAI HOSPITAL

*The Story of The Mount Sinai Hospital, of which the first ten installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninety-thirtieth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.\**

*The Jews' Hospital in New York was incorporated in 1852 by a group of public-spirited citizens, and in 1855 the doors of its first building on West Twenty-eighth Street were opened to receive patients. Staffed by some of the most prominent physicians of the day, the institution soon proved itself an excellent testing ground for the new methods and techniques which were being introduced into the rapidly broadening practice of medicine and surgery. During the Boyne Day riots, the cholera epidemic, and the Civil War, the Hospital showed its readiness to serve in time of crisis. In 1866 it was given its present name, The Mount Sinai Hospital. By this time it was outgrowing its first home, and in 1872 moved to larger quarters at Lexington Avenue and Sixty-sixth Street, where the expansion in organization paralleled the growth in size and in medical resources. Here, during the next few years the Out-Patient Department was formally established as an independent entity, the Medical Board was organized, the House Staff was enlarged, and the Medical and Surgical Services were separated for the first time. A number of new departments were organized, including New York's first Pediatric Service, under Dr. Abraham Jacobi, and in 1881 The Mount Sinai Training School for Nurses was established. Distinguished surgeons on the Staff and surgery as practiced by them during the early days of the Hospital on Lexington Avenue were sketched.*

### GROWTH AND DEVELOPMENT, 1870-1904

#### XI

The general interest of the profession in the scientific aspects of medicine and the growing employment of investigative methods was reflected in the constant references to Mount Sinai's need of a laboratory which appeared in the minutes of the Board of Directors and the Medical Board. But this interest in research developed slowly at first and had small beginnings. Before 1893 the nearest approach to laboratory work in the Hospital had been urinalysis, and that was done in the lounge provided for the Attending and House Staffs.<sup>83</sup> In 1891, as a result of considerable agitation on the part of some members of the House Staff, a special room was set aside for such tests, and urinalysis was performed "in a little arrangement rigged up with an alcohol lamp."<sup>104</sup> The room, however, was inadequate for any other work. In 1893 the Medical

\* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete are welcome and may be addressed to the Historian of the Hospital.

<sup>104</sup> Notes dictated by Dr. H. A. Cone, June, 1938.

Board expressed "their sense of the urgent necessity of the establishment of a laboratory."<sup>105</sup> In that same year the modest nucleus of what is now a most important and extensive part of the Hospital's work was organized.

Dr. Henry N. Heineman, Attending Physician, was appointed Pathologist and Frederick S. Mandlebaum, a graduate of the House Staff of 1891, was assigned to him as an Assistant. Dr. Mandlebaum, in the two years following his graduation from Mount Sinai, had studied in Berlin and Vienna under the leading pathologists of the day.<sup>100</sup> For six months after their appointment Drs. Heineman and Mandlebaum were a staff without a laboratory. As a consequence Dr. Mandlebaum did the Hospital's pathological work at his own office.<sup>106</sup> In December of 1893 Dr. Heineman announced his intention of donating laboratory equipment for the new department and five hundred dollars a year to pay the salary of his Assistant.<sup>107</sup> The Pathological Laboratory, as it was called for many years, found its first home on the second floor of the north wing, in a room "half the size of an ordinary hall bedroom"<sup>105</sup> which had formerly been the coat room for the students from the Nurses Training School.<sup>108</sup> Here two people could just manage to work at one time. This situation prompted the Laboratory rule which read that "there shall be no intrusion on the Pathologist or his Assistant." At one side of the room was an alcove, slightly above the level of the Laboratory itself, where committee meetings were often held. That early Laboratory was planned neither for privacy nor quiet, and the equipment of those days was far from perfect. The sterilizer leaked and could be used only if a broom handle, wrapped in cotton, were held against the hole.<sup>109</sup> The thermostat (there was only one) was heated by a gas burner which was considered a fire hazard. Therefore when cultures were being grown it was necessary for someone to sit up all night and watch the burner.<sup>71</sup>

Out of that small and badly equipped laboratory came an enormous amount of work. All gross material from the operating room and that obtained at post-mortem examinations was studied there. In the first two years of the laboratory's existence, Dr. Mandlebaum performed all post-mortem examinations. He did his own cutting of sections, staining of slides, and cleaning and sterilizing of test tubes. He even dusted the room itself and mopped its floor. White mice and guinea pigs were kept in the basement where the morgue was also situated. In the daytime the animals were brought out to the Hospital yard in their cages. There was no little excitement when a grocery cart upset the cages and the frightened animals scampered in and out among the equally frightened convalescents sitting in the garden.<sup>71</sup>

Despite all obstacles in that cramped room and the small one that was added

<sup>105</sup> Minutes of the Board of Directors' Meeting, The Mount Sinai Hospital, January 12, 1893.

<sup>106</sup> Libman, Emanuel: Notes on the History of the Laboratories of The Mount Sinai Hospital, prepared about 1932.

<sup>107</sup> Minutes of the Board of Directors' Meeting, The Mount Sinai Hospital, December 24, 1893.

<sup>108</sup> Interview with Dr. Morris Manges, May 30, 1939.

<sup>109</sup> Interview with Dr. Emanuel Libman, April 6, 1939.

to it in 1900,<sup>106</sup> significant scientific work was carried on. It was there that Dr. Mandlebaum, who became Pathologist when Dr. Heineman resigned in 1895, began the research on Gaucher's disease which was completed after twenty years.<sup>100</sup> There also the first studies in America of the Widal reaction in typhoid fever were made by Charles A. Elsberg, then Assistant Pathologist and a recent graduate of the Mount Sinai House Staff who later became an outstanding neurosurgeon and a member of the Consulting Staff. In that laboratory it was pos-



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sible to trace an epidemic of typhoid in the Training School to an employee who was probably a typhoid carrier.<sup>71</sup> There Emanuel Libman, leading diagnostician and bacteriologist, and member of the Hospital's Consulting Staff, began his valuable research on the heart condition, subacute bacterial endocarditis, which is often referred to as Libman's disease. Dr. Libman became Assistant Pathologist soon after his graduation from the House Staff in 1896. Later, when the Hospital had already moved to its present site, he became Associate Pathologist, a

position he held until 1923 and to which he brought the enthusiasm and imagination which to a large degree are responsible for the position the Mount Sinai Laboratories have achieved.

These were the men, who because of their convictions as to the significance of science in medicine, because of their willingness to give much time and effort not only to creative research but also to demands of the most routine matters, were responsible for making the meager laboratory a center of scientific activity and a source of inspiration, insuring Mount Sinai's progress. In this respect Dr. Arpad



DR. EMANUEL LIBMAN

Gerster's comment is particularly apt: "The Pathological Laboratory of Mount Sinai Hospital had an extremely small beginning. Its first perch was in a place not much larger than a bird's cage—that is, in a bay window in the north-west corner of the old Hospital. The birds inhabiting it were of the right breed."<sup>15</sup>

The year 1895 was marked by the announcement of Wilhelm Konrad Roentgen, Professor of Physics at the University of Würzburg, that he had found "a new kind of rays" which, although themselves invisible, could penetrate wood, paper, cloth, and—most amazing of all—human flesh. These rays could be used to "photograph" the metal or bones beyond such a barrier. The first reaction

of the medical world to this announcement of the X-ray was incredulity, closely followed by great enthusiasm. "Photographs" of human hands showing the bony structure beneath the tissue were common by 1896. But the discovery was considered largely an oddity and its implications were not immediately realized. The general public dubbed Roentgen's discovery "ghost pictures" and the common attitude of curiosity was not unmixed with humor, even indignation. Cartoons in the newspapers and popular weeklies forecast the fate of fashionable society when a photograph taken at a dance might reveal only a crowd of waltzing skeletons. Indeed, one worthy assemblyman in the New Jersey State Legislature introduced a bill "prohibiting the use of X-rays in opera glasses in theaters."<sup>110</sup> However, the fear of the medical profession that pictures of bones alone would be of no practical value was soon allayed, and within a few years after Roentgen's discovery X-ray machines came into general hospital use.

Mount Sinai purchased its first X-ray machine in 1900. For the first year it was chiefly in the hands of the House Staff, and the first plate was taken by Eugene Eising, the House Surgeon. The patient was a fat man and the exposure which took ten minutes revealed a fracture of his thigh. Some of the subsequent plates, however, failed to show fracture or bone breakage which had been discovered by clinical diagnosis. Within one year a separate department for X-ray work was established and Walter M. Brickner, a graduate of the House Staff and a member of the Surgical Staff of the Dispensary, was appointed "Radiographist." An article by Dr. Brickner in 1903<sup>111</sup> summing up the work of his Department indicates the great satisfaction felt even then when the X-ray findings were confirmed by clinical diagnosis, an operation, or post-mortem examination. Confidence in radiography increased rapidly so that seven years after the Department was founded and the Hospital had already moved to its present site, the Annual Report for 1908 includes the following comment:

"The services of this Department (radiographic) have been utilized to a much larger degree by the Surgeons and Physicians of the Hospital, and by the profession, and this Department is gaining in importance as the value of this service and its practical application in the practice of surgery and medicine are more largely recognized."

Since 1882 the reports of the Hospital Directors had indicated that the available space was inadequate for the demands made by the community on Mount Sinai. This condition had been somewhat improved by the alterations and additions already described as well as by the expanded facilities of the Dispensary and the creation of the District Service. The latter, organized in May, 1886, was known as the "District Corps of Physicians," and was the first medical serv-

<sup>110</sup> Glasser, Otto: Wilhelm Konrad Röntgen, John Bale Sons and Danielson, Ltd., London, 1933.

<sup>111</sup> Mount Sinai Hospital Reports, Vol. 3, 1903. (These reports are accounts of interesting cases written by members of the Hospital Staff. Volume I was published in 1898, Volume II in 1901 and the subsequent volumes, numbering five, came out every two years until 1907 when the publication was discontinued. These Reports, edited by Dr. Paul F. Mundé and Dr. N. E. Brill, may be considered the forerunner of today's *Journal of The Mount Sinai Hospital*, founded in 1934 and edited by Dr. Joseph H. Globus.)

ice of its kind in the city. Various districts were mapped out with a capable volunteer physician in charge of each district. Patients for whom there was no room in the Hospital, and who were unable to provide themselves with medical aid, were referred to these district doctors and were treated by them in their own homes until they could be admitted to the wards, or as frequently happened, until a rapid cure was effected. Nurses from The Mount Sinai Training School were assigned to this service, and medicines were prepared for the Hospital at cost by the best pharmacies in each district and were provided to the patient free of charge.

However the overcrowding of the Hospital was only temporarily relieved. The Annual Report covering 1887<sup>112</sup> points out that 597 patients were kept on a waiting list because there was no room to accommodate them. When room was available they were notified to that effect, but they failed to respond, probably because they had gone to another hospital. And just as there had been emergency demands on the little Twenty-eighth Street Hospital, so the larger Mount Sinai in its Lexington Avenue building was also called on to meet similar situations. On December 19, 1889, fire broke out in the Presbyterian Hospital, at Seventieth Street and Fourth Avenue. Mount Sinai, three blocks to the south, promptly took into its building forty of the patients, for "we rightly considered them as our neighbors and treated them as such."<sup>113</sup> The victims of the fire were cared for wherever there was space, in wards and private rooms. When American soldiers returned from the Spanish-American War in 1898, many of them were ill with typhoid fever and malaria. The Government had not sufficient hospital accommodations for these men, and Mount Sinai offered to care gratuitously for forty-four of them.

In 1893 the population of New York reached 1,800,000. This was twice what it had been when the Hospital moved to Lexington Avenue twenty years earlier.<sup>113</sup> The demands on public and voluntary hospitals increased accordingly. Moreover, in those twenty years more than 17,000,000 immigrants had come to the United States,<sup>114</sup> and the tenements of New York received a good proportion of them. Many of these men, women and children had "when sick neither the home nor the surroundings which provide hygiene, nourishment or nursing to insure good results."<sup>113</sup> Recognizing these conditions which were contributing toward the over-crowding of the Hospital, the Board of Directors, under the Presidency of Hyman Blum, resolved in 1893 to erect a new fireproof building on the same site Mount Sinai then occupied or on a new one. The new building was to have a bed capacity for three to four hundred patients. The problem was how to finance this plan.

Throughout the years spent in the Lexington Avenue building, the Hospital had received generous gifts: in 1882, the balance of a \$25,000 donation from Simon Abrahams; three years later, \$10,000 from Julius Hallgarten; from William Meyer, in 1891, the balance of a \$10,000 gift; by 1894, the aggregate of \$55,000

<sup>112</sup> Annual Report of the Directors of The Mount Sinai Hospital, 1887.

<sup>113</sup> Annual Report of the Directors of The Mount Sinai Hospital, 1893.

<sup>114</sup> World Almanac, 1937.

from Sarah Burr. But these contributions, liberal though they were, had been steadily drawn upon for the expenses necessary to run a hospital which year after year treated from 88 to 96 per cent of its patients free of charge. Therefore the new project required a special building fund. In 1893 bonds were issued and subscriptions began to come in.

At this point a new method of fund raising was proposed by Mr. George Blumenthal who had been elected to the Board of Trustees in 1892. (Mr. Blumenthal later served as Mount Sinai's President from 1911 to 1938 and as its distinguished President Emeritus until his death in 1941.) Convinced that raising



MR. GEORGE BLUMENTHAL

money by the issuance of bonds was an unnecessarily complicated process and that those who were willing to help the Hospital would be ready to donate money outright, he urged that the old system of fund raising be abandoned. Older members of the Board, more experienced in such matters, threw up their hands at such a proposal. Money had always been raised by asking donors to subscribe to bonds, and any other way would be considered odd by the people accustomed to the established plan. Moreover, payments had already been made on the bonds issued in 1893. Strong in his conviction that immediate collection of funds would succeed, Mr. Blumenthal pressed his view. He contended that the value of bonds already subscribed could readily be converted into outright donations,

and offered to speak to each subscriber himself. Moreover he prophesied that \$400,000 in cash could be raised in a short time. Finally, persuaded by the enthusiasm of this younger member, the Board consented to a six-week trial period and to be guided by the result. Before the meeting adjourned on that memorable Sunday morning, the Trustees themselves had pledged a total of \$140,000. Within four weeks the \$400,000 in cash donations was raised. The issuance of bonds then and there became an outmoded fashion of fund raising.<sup>115</sup>

After careful debate, the idea of erecting a new building on the Lexington Avenue site or of buying the property of the Chapin Home was abandoned. Land available for the new Hospital was under consideration for several years. It was finally announced in 1898 that "The Mount Sinai Hospital has agreed to purchase of plot of ground on the easterly side of Fifth Avenue between 100th and 101st Streets in this city, being 201 feet 10 inches on Fifth Avenue, running easterly 325 feet on both 100th and 101st Streets, making one plot 201 feet 10 inches  $\times$  325 feet."<sup>116</sup>

By 1904, the year in which the Hospital moved to 100th Street, the enlargement of the Staff and its increasing departmentalization were indicative of plans for a Mount Sinai of wider scope. In that year, Sigismund S. Goldwater, a graduate of the House Staff of 1902, was appointed Superintendent (the title is now Director) of the Hospital—the first medical man to hold that position. Commissioner of Health of New York City in 1914, Commissioner of Hospitals from 1934 to 1940, and subsequently President of the Associated Hospital Service of New York, he gained an international reputation as a hospital planner and administrator. In the twenty-four years he spent as Director and Superintendent of Mount Sinai he brought to his work a vision and foresight which played a major role in its development.

In the year of the Hospital's removal to 100th Street, its Consulting Staff numbered four. The Physicians were Dr. Jacobi and Dr. Janeway, who had resigned from the Attending Staff seven years before. The Surgeons were Dr. Stimson and Dr. Fluhrer who in 1900 had resigned as Attending to the Genito-Urinary Service. There were now four instead of three Attending Physicians on the Staff: Drs. Brill, Manges, Meyer, and Rudisch. Drs. Brill and Manges had been appointed Attending Physicians in 1898. The number of Adjunct Attending Physicians had been doubled so that there was now an Adjunct for each of the four medical services. The Attending Physician to the Children's Service was Dr. Koplik who had succeeded Dr. Scharlau when the latter resigned in 1900. There was still only one Adjunct on the Children's Service.

The Attending Surgeons in 1904 were Drs. Gerster and Lilienthal. Dr. Lilienthal had been appointed an Attending in 1899. For the three preceding years Dr. Gerster had been the only Attending Surgeon, since Dr. Wyeth had resigned because of ill health, Dr. Stimson had joined the Consulting Staff, and Dr. Fluhrer had been Attending only to the Genito-Urinary Service. There were four Adjuncts on the Surgical Staff in 1904 instead of the former two. Two Gynecological Services had been established, one under Dr. Brettauer who had

<sup>115</sup> Interview with Mr. George Blumenthal, December 27, 1939.

<sup>116</sup> Minutes of Board of Directors' Meeting, The Mount Sinai Hospital, February 15, 1898.

become Gynecologist at the death of Dr. Mundé in 1902; the other under Florian Krug, who since 1888 had been Gynecologist to the German (now Lenox Hill) Hospital,<sup>117</sup> and in 1903 had been appointed to the Mount Sinai Staff. The Genito-Urinary Service, which had been suspended as a separate division when Dr. Fluhrer joined the Consulting Staff, was reestablished in 1902 under the direction of Hermann Goldenberg. An Adjunct was appointed to this Service for the first time. Dr. Goldenberg had served as chief of one division of the Dermato-



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logical Department of the Dispensary since that Department's organization in 1890, and he went on with this work for many years, even after his appointment to the Genito-Urinary Service. In 1911 he became Attending Dermatologist to the Hospital, and as Consulting Dermatologist continued his services to Mount Sinai from 1929 until his death in 1937.

By 1904, the Neurological Service under Dr. Bernard Sachs and the Dermatological Service under Dr. Lustgarten each had acquired an Adjunct. The Eye and Ear Service under Dr. Gruening now had two Adjuncts instead of one. A

<sup>117</sup> Mayer, Max: Report of the Gynecological Department of The Mount Sinai Hospital, January, 1939.

separate department had been created for diseases of the throat, and Dr. Bryson Delavan became Laryngologist to the Hospital in 1903, an entirely new position. Dr. Delavan had been chief of the Children's Department of the New York Dispensary as well as of the Department of Clinical Medicine there. From 1878 until 1883, he had been Curator of the Museum and Assistant Pathologist at the New York Hospital, and from 1887 Professor of Laryngology and Rhinology at the Polyclinic.<sup>118</sup> When the new Laryngological Service was established at Mount Sinai, an Adjunct was also appointed to it. The Radiographic Department under Dr. Walter Brickner had had an Assistant since 1902. In that same year two anesthetists were appointed. Before this, members of the House Staff administered ether, for such work had not been regarded as needing special training.

The Laboratory Staff, by 1904, also showed signs of expansion. Dr. Mandlebaum was Pathologist, and continued in that position until his death in 1926. A Physiological Chemist, Samuel Bookman, was appointed in 1904. Dr. Bookman continued in that capacity on the Laboratory Staff until 1927, when he became Consulting Chemist. In addition to an Assistant Pathologist, there were appointed to the Laboratory an Assistant Physiological Chemist, a Second Assistant Pathologist, a Laboratory Assistant, and a Pathology Intern.

Like the rest of the Hospital, the Training School for Nurses was displaying growth. Its student body in that year numbered eighty-five, with ten probationers. This is in striking contrast to the eight probationers who formed the School's first class in 1881.

When the Mayor of New York laid the cornerstone of Mount Sinai's Lexington Avenue building in 1870, the inscription on the trowel which he had used read "Beth Cholim," or "home of the sick." Essentially, to be a home of the sick is the function of every hospital. In 1870 Mount Sinai was such a home rather than a scientific institution. There was no formal Medical Board to administer medical matters, no division of the fundamental services, no organized Dispensary, no separation of departments treating diseases that require specialized knowledge, no division of research and investigation, no system for the training of young men. But slowly the medical scene changed, and in the thirty-two years spent on Lexington Avenue the Hospital changed with it. On the Mount Sinai Staff were many pioneers who led the gradual progress toward a more scientific approach in medicine. For, roughly, those thirty-two years were a period in which the whole concept of scientific medicine had taken form. The basic and gradual growth which marked those years at Mount Sinai paralleled that which took place in the medical world at large, and served to lay the foundations essential for a mature, scientific institution in the years to come.

This installment concludes the first and second sections of the Story of The Mount Sinai Hospital. The third section is now in preparation and will be published in the *Journal of The Mount Sinai Hospital* from time to time as the material becomes available.

<sup>118</sup> National Encyclopedia of American Biography, Current Series.

## Benjamin Mordecai

December 9, 1865–August 3, 1943

It is with profound sorrow that the Board of Trustees of The Mount Sinai Hospital has learned of the untimely death of its friend and colleague, Benjamin Mordecai.

For more than twenty-four years he served the Hospital with great devotion and gave unstintingly of his time and means. He always evinced the greatest interest in the various affairs of the Hospital. For many years he was Chairman of its Building Committee and under his wise guidance, many modern buildings were added to the Hospital during the past two decades.

His warm and genial personality endeared him to all those with whom he came in contact and his presence will be greatly missed.

To his bereaved family the Board of Trustees extends its heartfelt sympathy.

WALDEMAR KOPS, *Acting President*  
GEORGE LEE, *Secretary*

### AN APPRECIATION\*

Friends,

How fitting it is that Benjamin Mordecai should spend his last hours on earth in this sanctuary in the midst of his loved ones. Long before this Temple was a reality, it was envisioned in his mind. He saw its walls grow stone on stone and row upon row. This place will remember him for the spirit of dedication that he brought to its building. Other places, consecrated to the enrichment and enlargement of life will also remember him for his imagination, for his vision, for his enterprise. So much of his life was given to lighten the burden of others, to bring healing to those who were in pain, to bring help and guidance to the afflicted. So much of his life was given up to changing waste places to places of growth, to changing the broken down area of the earth to places that tower with things of beauty and usefulness.

Mr. Mordecai had a high sense of duty. He came upon it not by accident. He saw it in the home of his father. He saw it in the example of his grandfather's life. For both his father and his grandfather had served gallantly and loyally and sacrificially in the early years of our nation's history, and so Mr. Mordecai in his own lifetime gave of his wisdom and his knowledge, gave of his means and his strength, gave of his loyalty to so many institutions that enriched and exalted the lives of those who could not always make their own way. He did not do these things for self aggrandizement because he was a person of great reticence, a person almost shy—not seeking the honors that people might want to pay him.

He was a man of the utmost integrity. He set for himself high standards of right, truth and goodness and by these standards he walked and talked and

\* Delivered at the funeral service of Mr. Benjamin Mordecai at Temple Emanu-El, August 6, 1943.

dealt with his fellowmen. Just as he won their gratitude for his goodness, so he enjoyed their confidence and trust for the standards of right by which he lived.

All the time that he was building in a public sense, he enjoyed gracious living in the private dwelling of his own family life. How shall one speak of the great love that filled his heart, the love that was manifest in his every relationship, in the perfect union that bound him throughout the years as the loving mate of her who left him for life eternal almost to the day twenty years ago; years that were kept fresh and green in his own memory, through the love that dwelt in his heart. To his sons and daughters, to his grandchildren and now great grand-children, he was not only loving father, but wise counsellor, good companion and understanding friend. He shared in their joys and sorrows. He was a part of their hopes and dreams and aspirations. He was always deeply concerned about every moment of their being.

His was a blessed life. Well-born, he never lost the common touch. Privileged to walk with men in high places he yet clung to the simple tastes of the life that he learned in the home of his father. Blessed always with robust health, he used his strength to add strength to others. So he lived and wrought and built and the places that he built will remember him for the quiet generous spirit that he brought to everything. All that he touched will remember him for the loyalty and devotion that he brought to every trust.

Rabbi N. A. Perilman

## Hugo Blumenthal

February 7, 1852–August 8, 1943

It is with profound sorrow and regret that the Board of Trustees of The Mount Sinai Hospital has learned of the death of its beloved colleague and friend, Hugo Blumenthal.

For over forty years, beginning with his election as Trustee in 1902, he gave unstintingly, not only of himself but also of his means.

His greatest contribution to the development of this Institution was his interest in The Mount Sinai Hospital School of Nursing. During his Presidency of a quarter of a century, it grew from modest proportions to one of the leading nurse-training schools in the country.

His generous financial support made possible many activities which otherwise would have been impossible of accomplishment. His genial and sympathetic personality endeared him not only to his fellow Trustees, but to all those who knew him.

To his bereaved family, the Board extends its most heartfelt sympathy.

WALDEMAR KOPS, *Acting President*

GEORGE LEE, *Secretary*

In the passing of Hugo Blumenthal, a pall of sorrow and regret has fallen upon the Board of Directors, the Faculty and the Student Body of The Mount Sinai Hospital School of Nursing, of which he served as President for twenty-five years and was serving as Honorary President at the time of his passing.

While the vast progress made by the Institution during his Presidency, was due to his vision and expert knowledge, it was his personal characteristics of kindness, consideration and friendship that endeared him to all with whom he came in contact. His fellow Directors and the members of the Faculty always found his sage advice, tempered with softness, a staunch staff upon which to lean and depend. All feel a deep and personal bereavement.

To his sorrowing family, the Directors and Faculty Members extend their heartfelt sympathy.

ALFRED L. ROSE, *President*

HAROLD D. WIMPFHEIMER, *Secretary*

## A TRIBUTE\*

A dearly beloved friend is gone.

We meet this morning with a sense of great loss. When one's heart and emotions are so deeply involved in the passing of a friend, it is difficult to express the grief and bereavement for one and all the nurses. It was Mr. Blumenthal's own wish that a farewell be said by one with whom he worked.

To those who knew him and his works this is a time when memories crowd in of his great love and interest—the school and his nurses. Twenty-five years was he active as President of The Mount Sinai Hospital School of Nursing, —twenty-five years during the school's greatest growth and development. His wise leadership, his tireless service, and his devotion to the best in nursing education and nursing care to patients, brought the school to the high place it holds in nursing today.

Mr. Blumenthal was beloved by all. He had an unusual personality, charming, delightful, dignified, but always approachable, full of kindness, human in every respect. To the faculty, graduates and student body he was a kindly adviser, a dear friend and an inspiration. We will never forget his greatness of heart, and the personal interest he manifested in all.

Thousands knew him—thousands mourn him. Although his life is past, his ideals and standards of service will live forever and be cherished by our school. We will miss him sorely, and we share with his family and many friends a deep sorrow in the loss of an accomplished leader, an honored citizen and much beloved friend.

G. A. W.

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\*Delivered at the funeral service of Mr. Hugo Blumenthal by Miss G. A. Warman, Principal of the School and Superintendent of Nurses of The Mount Sinai Hospital.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Some Shakespearcan Characters in the Light of Present-day Psychologics.* I. S. WILE. *Psychiat. Quart.* 16: 62, January 1942.

The truth of human psychology is an essence, the theories of it vary with the ages and current theories of activity. Shakespearcan characters are employed to demonstrate that they may be approached as delineated from any angle of theory without hesitancy to prove its worth as supporting a contemporary mode of thought. Characters emerge from comedies, tragedies and histories to indicate their adequacy as examples of the current concepts of Freud, Jung, Adler, Rank, Watson, Wertheimer and many others.

There is no pleading for a standard mode of psychological interpretation but an exposition of a method of teaching psychology through literature and clarifying literary characters by reference to the various schools of psychological thought.

*X-Ray Protection in Diagnostic Radiology.* C. B. BRAESTRUP. *Radiology.* 38: 207, February 1942.

Without proper precautions diagnostic radiology presents definite radiation hazards. Even with modern "ray-proof" equipment there is the possibility of over exposure to the patient and harmful stray radiation to the personnel. Tables are presented showing the dose delivered to the patient during fluoroscopy and radiography. Figures are also given for the stray radiation received by the staff during fluoroscopy, cystoscopy, fracture setting and radiography, including dental. The author advocates the periodic use of dental films as indicators of excessive stray-radiation. The recommended safeguards should be of interest also to the physicians not specializing in radiology, but still using roentgen rays for diagnostic purposes. A brief discussion is presented also on x-ray protection in the rapidly expanding field of industrial radiography.

*Cavum Septi Pellucidi Biloculare.* M. H. POPPEL. *Radiology* 38: 361, March 1942.

The septum pellucidum is a thin vertical partition composed of two thin laminae in apposition with each other in the median plane. On the encephalogram it is represented by a well demarcated vertical linear shadow about 2 or 3 mm. in width, interposed between the lateral ventricles in the sagittal views.

When the laminae are separated there results a cavity of the septum pellucidum, also known as the fifth ventricle. Apposition of the fornix to the corpus callosum subdivides this fifth ventricle into an anterior portion, for which the name of fifth ventricle is retained, and a posterior portion called the sixth ventricle.

A case is described in which the cavity of the septum pellucidum was biloculated as result of a vertical midline adventitious partition.

*Contrast Visualization of the Heart and Great Vessels in Emphysema.* M. L. SUSSMAN.

M. F. STEINBERG AND A. GRISHMAN. *Am. J. Roentgenol.* 47: 368, March 1942.

By angiocardigraphy, using a multiple exposure technique it was found that in 24 out of 28 unselected cases of emphysema of various types and grades, there was some evidence of right ventricular dilatation or dilatation of the base of the pulmonary artery. In 50

per cent of these, or 43 per cent of the total, dilatation of the right ventricular cavity was unequivocal and the interventricular septum was convex to the left (in normal individuals, the septum is convex to the right).

In this rather small series, right axis deviation or interventricular block of the type described by Wilson was constantly associated with abnormalities of the right cardiac chambers. The normal electrocardiogram did not preclude the findings of right ventricular ventricular dilatation. On the contrary in eight cases, well-defined dilatation with deviation of the septum was present. The lack of right axis deviation in some of these cases might be accounted for by the coincidental presence of left ventricular enlargement.

In two cases of marked emphysema with chronic bronchitis of long duration, there was no right ventricular dilatation. No explanation is offered for this finding. In two other cases in which a normal right heart was found the clinical symptoms and normal vital capacity suggested extremely mild involvement.

Coincidental left ventricular dilatation could be accounted for in many instances by essential hypertension or previous coronary thrombosis. In the remaining cases coronary sclerosis seemed to be the most likely explanation.

*Remarks on the Psychopathology of Pornography.* W. ELIASBERG. J. Crim. Psychopathol. 3: 715, April 1942.

Pornography is much more often found in private letters and notebooks than in printed products. Pornography is a characteristic symptom of psycho-sexual immaturity often occurring with narcissistic symptoms. Not so seldom handsome men, beautiful women or beautiful children are found among its producers and consumers. The symptom may lead to the discovery of frigidity on the part of the woman or individualized impotence on that of the male. The symptoms should never be treated in an isolating manner.

*Tumors of the Aqueduct of Sylvius: Blastomatous Formations of Varied Origin, Limited to the Mesencephalon.* J. H. GLOBUS, H. KÜHLENBECK, AND D. WELLER. J. Neuropath. & Exper. Neurol. 1: 207, April 1942.

The four instances of blastomatous formations of the aqueduct of Sylvius studied in this paper belong to three different groups.

Cases 1 and 2 represent tumors of mesodermal origin. We regard these tumors as true vascular neoplasms and consider the very variable degree of participation of neuroectodermal tissue in between the vascular loops to be a secondary feature.

In order to find a possible clue as to the derivation of these hemangiomas in the region of the aqueduct, a careful survey and review of the ontogenetic development of the midbrain was made. However, this survey failed to disclose any feature which would explain the particular location and mode of development of these neoplasms. It may be mentioned that the blood vessels supplying the central gray matter around the aqueduct enter the brain partly from the base, through the interpeduncular fossa and partly dorsally, from the surface of the quadrigeminal plate, forming a dense capillary network, especially in the oculomotor region. It might be of significance that the vascular apparatus protrudes into the ventricular system, forming a choroid plexus, in all subdivisions of the brain except in the midbrain. Of all vertebrates only *Petromyzon* shows also a typical choroid plexus of the mesencephalic ventricle or primitive aqueduct (Kühlenbeck). Whether a suppressed but still latent factor of phylogenetic origin plays a rôle in the tendency of vascular formations to invade the aqueduct is a moot question.

The tumor in Case 3 is a mixed ecto- and mesodermal blastoma, representing an autochthonous teratoid growth and belongs to the category of pinealomas. The tumor displays the characteristic mosaic-like features analyzed in the studies of Globus and Silbert and presumably took its origin from an ectopic embryonal rest in the vicinity of the normal pineal body.

The neoplasm in Case 4 is of purely ectodermal origin and represents an example of the type designated as glioneuroma by one of us. The significance of the subependymal cell

plate as the source of origin from tumors of this type has been pointed out by us elsewhere and these observations are fully substantiated by our findings in this case. In the light of our studies the cases of occlusion of the Sylvian aqueduct described by Orton, Kernohan and some cases of stenosis described by Sheldon, Parker and Kernohan, and by Roback and Gerstle should also be interpreted as products of proliferation resulting from localized or diffuse spongioblastosis and spongioneuroblastosis in the subependymal cell plate, but exhibiting a faulty advanced stage of differentiation.

*Hamartial Nature of the Tuberous Sclerosis Complex and Its Bearing on the Tumor Problem.*

S. E. MOOLTEN. Arch. Int. Med. 69: 589, April 1942.

A case of the tuberous complex in a girl aged 20 is described. The disease was first brought to light clinically by hemorrhage from a renal hamartoma. The latter was of striking appearance but typical histologic structure and contained a large angiomatous component and a caliceal anomaly. The patient also presented adenoma sebaceum, phacoma of the retina and clinical evidences of typical cerebral involvement. The course of her later illness resembled that of a tumor involving the brain stem in the region of the left corpus quadrigeminum and aqueduct of Sylvius. Left ophthalmoplegia with Argyll-Robertson pupil were present, also papilledema and other evidences of internal hydrocephalus.

The tuberous sclerosis complex may be epitomized as a disseminated disease, often hereditary in type, characterized by numerous defects in tissue combination (hamartia). The brain, heart, retina, kidneys and skin are conspicuously affected. The individual lesions range in size from microscopic foci (hamartial "germs") to visible nodules (hamartomas) having a superficial resemblance to neoplasms. Developmental defects of a more serious type, such as cardiac or renal anomaly and so-called stigmas of degeneracy, often coexist and corroborate the view that the disease has its inception in the earliest stages of embryonal development.

Malignant neoplasms supervene with extreme rarity in the somatic foci of the disease and are slow growing and produce few metastases. In the cerebral foci, however, such tumors appear to occur much more frequently, taking the form of a malignant mixed tumor (neurospongioblastoma), which is often multiple.

The concept of a defective mechanism of induction by embryonic organizers (Spemann) offers a logical explanation of the pathogenesis of this disease and of the accompanying developmental defects. There is much reason to believe that the same principle underlies the latter complication of malignancy, especially in the brain. In a study of this disease as a type it is possible to derive certain generalizations which have application to problems of more general importance, chiefly the genesis of congenital dysplasia and the predisposition to tumor. The embryonic systems of organizer action are probably the initial phase of certain basic mechanisms of cellular integration which normally govern differentiation and maturation of proliferating cells throughout life. Excessive fibrosis, aging and preexisting malformation are factors which evidently impair such control and thereby predispose to malignancy. Neurotrophic influences are apparently also important in the maintenance of the organizer field, and the predisposition to brain tumor in tuberous sclerosis is probably only one of many instances in which defects in neural integration underlie the predisposition both to anomalous overgrowth and to neoplasia.

The similarities between the tuberous sclerosis complex, multiple neurofibromatosis, encephalotrigeminal angiomatosis, Lindau's disease and related syndromes are sufficient to establish them all as forms of disseminated hamartiosis. The latter term may be employed as a general category of classification for syndromes such as these in order to emphasize their non-neurologic features.





Shepard Knepper.



## ALFRED MEYER

## AN APPRECIATION

IRA COHEN, M.D.

[*New York*]

Most men are quickly forgotten after even a brief absence from their usual haunts. Some few, for one reason or another, so impress their personality that no matter how long the absence revisits are reunions. This spirit of reunion prevails even though the participants may never have met before. The mere mention of the visitor's name calls to mind facts and legends associated with it.

Such a man is Alfred Meyer. From the days of his internship in The Mount Sinai Hospital, which began in 1877, upon his graduation from the College of Physicians and Surgeons, until his retirement from active duty as Attending Physician in 1919, he was an active constructive force in the life of the hospital. During that period the institution changed physically from the outmoded buildings on Lexington Avenue between Sixty-sixth and Sixty-seventh Streets to those it now occupies; it expanded from a single medical and surgical service to its present multi and special service organization. That period saw the first use of trained nurses and the establishment of a training school for nurses. In that period bacteriology came into its own and surgery passed through its antiseptic to aseptic technique.

Through thirty-five years, from 1884 to 1919, as Attending Physician, Dr. Meyer conscientiously directed his constantly growing service. At the bedside he was always the teacher. Above all he taught by precept thoroughness and attention to detail. The case histories would be supplemented by his own searching questions, and physical signs noted by his keen senses of sight, touch, sound and even smell. When baffled by some puzzling case he would review it as though seeing it for the first time. Often completely engrossed in his rounds, time, appointments and waiting private patients were completely forgotten. It should be recalled that demands of an active practice were not so readily met in the days before telephones and automobiles. For some twenty-five years of this time Dr. Meyer's practice was limited to consultation work. His energetic participation in the tuberculosis movement in the community, his medical writings almost entirely limited to this field, and his unfailing ability to be of service when called in consultation led to his recognition as an authority in pulmonary conditions.

It is not only his purely medical activities that have left their imprint on the history of the hospital, but also his wise counsel and unselfish devotion to its welfare. For fifteen years he served as Chairman of the Library Committee thus giving of his time as he had given of his means. It was he who had recognized the needs of the house staff for a library close at hand so that precious time would not be wasted in travel. To this end he sought contributions of others and gen-

erously headed the list to establish the library. He was Chairman of the Training School Committee which in those days meant the medical care of sick nurses. While thus serving, an unreported illness in the school led to a typhoid epidemic in the training school which so wore him out that he had to take a prolonged rest. For seven years he served as secretary of the medical board which at that time meant the actual physical writing of the minutes.

At the Montefiore Home, now known as the Montefiore Hospital for Chronic Diseases, he is remembered for his work in their tuberculosis sanatorium at Bedford Hills. In 1899 he was appointed Attending Physician to that branch of the hospital. In these days of good roads and fast automobiles, it is well to recall that then the weekly visit by train meant the sacrifice of the better part of a day.

To demonstrate the technique of artificial pneumothorax therapy, Dr. Meyer invited to Bedford Dr. Cleveland Floyd of Boston who had studied under Forlanini of Italy. He introduced work therapy at the sanatorium. Patients had their individual vegetable garden plots, serving as a therapeutic measure and a useful purpose to the hospital. In 1919 Dr. Meyer was made a consultant at the Montefiore Hospital.

To those of us associated with The Mount Sinai or Montefiore Hospitals it seems but natural to think of Dr. Meyer in connection with his work at these institutions. But to many his name is synonymous with one of the pioneers in the field of tuberculosis. A mere recital of his connection with and offices held in the national and local societies gives but little inkling of the enthusiastic work and the energy he devoted to them, and to the tuberculosis movement. In the National Tuberculosis Association he was elected a Director at their second meeting in 1906 and served to 1921, was Vice-president in 1918 to 1919, in 1923 he was made an honorary member. He served as a member of a small committee which arranged for the International Congress in Washington in 1908. Prior to that date, in 1906, he traveled in Europe to stimulate interest in and make arrangements for the Congress. Following the meeting in Washington he single-handedly collected \$30,000 to bring the exhibit to New York where it was viewed by some 750,000 persons at the Museum of Natural History. Ironically he was not one who saw it. The effort expended in bringing the exhibit to New York taxed his strength and resulted in a break down. In 1906 he became a member of the Committee for the Prevention of Tuberculosis of The Charity Organization Society. In 1919 he was one of the incorporators and first directors of the New York Tuberculosis Association. He still serves as a director. In March 1942 this association awarded him a testimonial of appreciation for his many years of devoted service. In presenting this Dr. Burns Anderson stated: "It may therefore be said that the work and influence of Dr. Meyer in this field has covered half a century during which the impact of his energy, his courage and his great zeal for the prevention and control of tuberculosis has been felt not only in our own city but in this state, throughout the nation and indeed throughout the world."

When in 1899 Dr. Meyer was appointed the visiting physician to Bedford the Country Sanatorium of the Montefiore Home, a small altered farm house

sheltered the patients. New buildings were contemplated. Dr. Meyer actively participated in all deliberations of the building committee. The cottage plan of Trudeau's Sanatorium at Saranac Lake was advocated by some. Dr. Meyer opposed this on the ground of cost, and more important, the social characteristics of the patients to be cared for. His viewpoint prevailed.

By dint of hammering, hard work and much correspondence and with the co-operation of The Charity Organization Society, The Association for Improving Condition of the Poor, The St. Vincent de Paul, United Hebrew Charities and the State Charities Aid Society, Dr. Meyer was responsible for meetings at the



FIG. 1. He was a bit taller than his present 5 feet or so and probably a few pounds heavier. His beard, trimmed somewhat closer, was not always white but most of us cannot recall it otherwise.

New York Academy of Medicine which finally resulted in the establishment of the Municipal Sanatorium at Otisville in 1906. Apropos of this work, Dr. Herman Biggs stated in a letter to Dr. Meyer that New York City would never be able to repay to Dr. Meyer its debt of gratitude.

Nor is the State less indebted to him for his efforts in the establishment of the sanatorium at Ray Brook. After the introduction of the bill for its establishment in 1900 he appeared before a joint committee of the Senate and the Assembly at Albany to advocate its passage. He enlisted the aid of Gov. Theodore Roosevelt, who better than his promise to sign the bill, should it be passed, actually worked to have it reported out of committee when it seemed likely to die there. Nor did the interest of Dr. Meyer end there, but on behalf of the five

New York charity organizations he inspected and in a written report condemned the proposed site near the Dannamora Clinton Prison. Finally the sanatorium was established at Ray Brook and New York State was second only to Massachusetts in establishing a State Hospital for its tuberculous poor. The hospital opened in July 1904.

A similar recounting could be made in connection with the selection of the site of Sea View Hospital. He was chairman of the Research Advisory Board of the



FIG. 2. Though a thoroughly finished pianist and a lover of music, this cannot be called one of Dr. Meyer's hobbies. It is a part of his life as much as the practice of medicine.

National Jewish Hospital for Consumptives. Is it any wonder that Mayor Seth Low exclaimed at the laying of the corner stone of the present building of Mount Sinai that if the hospital had been responsible for nothing else but the development of Dr. Meyer it would have justified its existence.

Let us look now at the man who so devoted himself to two large hospitals, to an active practice and who is a pioneer in the modern tuberculosis movement. When today in his ninetieth year an erect, bright eyed, alert, quick moving, white-haired gentleman is seen, it does not tax the imagination to picture him as he was twenty or even forty years ago. He was a bit taller than his present

five feet or so and probably a few pounds heavier. His beard, trimmed somewhat closer was not always white but most of us cannot recall it otherwise. The lines of his face in repose are etched by his frequent kindly smile. The smile which is friendly in greeting or appreciative of humor, the meaning of which can be read in the expression of his eyes. The eyes which see completely through sham but follow with understanding interest every word and action of the person to whom he is speaking. His hands might readily deceive one, they seem to be in such restful relaxation. Yet in action they brought out in chest percussion, clear notes, free from overtones, or on the piano keys they show strength or zephyr touches as the master musician commands. Though a truly finished pianist and a lover of music this cannot be called one of Dr. Meyer's hobbies. It is a part of his life as much as is the practice of medicine. Truer hobbies are his intimate knowledge of wild life,—birds, trees, plants he knows them by their scientific and popular name. An ardent lover of nature for more than twenty-six years his vacations were spent "roughing it." He was a member of the Adirondack League Club. He would tramp the wilderness without guides—carrying his own boat albeit it was a specially built light one. A twenty-five mile trip in a day was not infrequent. On such trips his companion was his wife. She did her share in carrying the pack, as she has done her share throughout more than fifty-six years of married life in sharing the burdens and the honors. The influence such companionship and understanding had on Dr. Meyer's life is not for such an article as this, if any. It is too sacred to pry into, yet too profound not to be acknowledged.

In action, in the practice of his profession he was at once an inspiration and an example to the younger men, a never failing aid to his colleagues, and a true comfort and healer to his patients. The latter to him were not mere cases presenting medical problems, but sick human beings to be eased of their unbearable burdens. From the scientific side the details of the illness were stored in Dr. Meyer's retentive memory to be called out when needed to help clarify some other similar problem, perhaps years later.

Those of us who went to the clinical conferences at The Mount Sinai Hospital of thirty years ago recall how each one was attended by the heads of the services, and how each "Attending" would discuss the case presented in his own field. We used to marvel at the minute details of the illness of patients of twenty or more years ago which Dr. Meyer would cite in support of his point of view. He would recall the history, the physical findings, and the laboratory studies.

In all such discussions as well as in administrative matters, Dr. Meyer was ready to stoutly defend his opinions, but one sensed his tolerance of the other person's point of view. Tolerant, except when it is a question of right or wrong, then there is no compromise on his part. Today as then he believes in prompt action, especially in doing good. In calls made upon him for contributions to a worthy cause, he is not only charitable but generous. Nor does he await the call of organizations, many unsolicited donations are made to those in need of help. This could not be otherwise, for his life has been and is guided in civic movements, in the practice of medicine and in his private dealings by a profound love of his fellow-man.

## THE MECHANISM OF LUNG CLEARANCE AND SOME PRACTICAL IMPLICATIONS

JESSE G. M. BULLOWA, M.D.\*

*[Clinical Professor of Medicine, New York University College of Medicine; Visiting Physician, Harlem Hospital and Willard Parker Hospital, New York]*

The lungs hang suspended from the lower pharynx as if designed to receive the pharyngeal contents. These contents enter the esophagus during deglutition because the larynx is covered by the accurately adapted beak shaped epiglottis. When the epiglottal mechanism fails during swallowing due to chilling of the extremities or from other causes, the epiglottis becomes a funnel and the lungs receive pharyngeal or nasal pharyngeal contents. It has been observed roentgenologically in sleeping people and with the bronchoscope after tonsillectomy that the aspirating force of the thorax is sufficient to draw fluids into the trachea and bronchi even when the patient is horizontal (1). The tracheo-bronchial tree may also contain fluid entering from the alveoli either by failure of lymphatic drainage or by inadequate venous return and in addition the lung parenchyma may be contaminated by blood borne infection which may extend to the alveoli and bronchioles. By whatever paths infection or fluid reach the bronchioles they must be destroyed and be disposed of by adequate drainage either to the outside or into the lymphatics or into the blood stream.

Drinker and Warren (2) have recently shown the importance of lymphatic drainage through the right lymphatic duct in maintaining clear alveoli. Pulmonary edema may result from occlusion of the lymph channels produced by coagulation of the contained lymph when there is liberation of large amounts of prothrombin as occurs when much tissue has been damaged in extensive pneumonias or in gas poisoning. Organisms entering the lungs via the airways may be destroyed by lysozyme present in the fresh mucus.

It is difficult to infect the lungs of dogs and other quadrupeds with pneumococci in fluid media or to keep a foreign body in their bronchial trees. Their bronchial tree is inverted in their ordinary position of rest and sleep and its branches are acutely funneled so that anything introduced is quickly moved forward and drops out. It is only when prolonged contact with the mucous membrane is maintained that the bronchi become infected. This is accomplished by injecting the cultures in a viscous medium of mucin which fills smaller tubes.

Whenever fluid or contaminants reach the bronchioles either from the alveoli or having passed the larynx from the tracheo-bronchial tree devices which are designed to effect clearance of the passages are activated. Some of the similarity of structure and performance of the alimentary and respiratory tract is due to the origin of the respiratory tract as an outgrowth of the gut. The surfaces of both respiratory and alimentary passages are covered by a continuous mucus film. In the tracheo-bronchial tract the mucus comes either from surface goblet

\*Deceased November 9, 1943.

cells or from the racemose glands which occur in the membranous segment opposed to the esophagus and in the intercartilagenous rings. The ciliated cells may under irritation or anoxia become muciparous goblet cells. The mucus in the tracheo-bronchial tree fuses into a tubular sheet which is confluent with a descending sheet starting from the extensive Schneiderian membrane which lines the nose and accessory sinuses (3). The mucus sheet, continuous with the pharyngeal mucus, is under constant traction increased with each swallowing act. These sheets are the prototype of the belt conveyer for they bear on their surfaces the contaminations to be removed. There are several devices to insure the continuous progress and renewal of the mucus sheet. Delay or stoppage of movement leads to interruption of the belt and causes inspissation of the mucus. While continuous transit of the mucus is maintained the lungs are continuously cleared.

If one examines the gastric aspirate or vomitus of children with respiratory infections who have had much water to drink two sorts of mucus masses are frequently found floating in the clear fluid. One from the upper respiratory tract is a thin film which is a cast of the posterior nares, nasal and oropharynx. The other is a folded taut glistening greenish film, a cast of the larynx, trachea and of the inverted or folded bronchi.

It is worthwhile detailing the circumstances under which the function of this mechanism is either depressed or augmented. The mucus is increased by inflammation of the glands or the walls of the bronchi and its subdivisions. Inflammations of the lung may commence in the alveoli as in certain lobar pneumonias when the increase in mucus may be very scant and the patient is often unaware of any increase. He does not cough and the exudate when it reaches the larynx is swallowed. The amount of secretion from the glands is diminished by atropine and its congeners. Our definite knowledge concerning the control of pulmonary mucus is meagre.

Unless the mucus sheet constantly progresses upward and is swallowed it rapidly desiccates and cracks into a tile-like lining of which portions may temporarily obstruct the openings of small bronchi as they pass. Because of this mucus desiccation it is customary to cleanse the inner cannula in the treatment of tracheotomized patients at hourly intervals and to inject a solution of bicarbonate of soda into the trachea and to aspirate mucus thus softened to prevent retention and excessive inspissation with obstruction.

The tracheo-bronchial tubes are in constant movement thus preventing adhesion of the mucus tube or sheet to the cells or glands from which they are derived. The bronchial tubes are enlarged and lengthened with each inspiration and with each expiration they are shortened and contracted again resulting in shifting of the mucus. To prevent compression of the tissues between the bifurcating bronchi during these changes the anterior portion of the lung creeps forward on the thorax. To facilitate the enlargement of the lobes they are divided into two great halves, an upper anterior portion and lower posterior portion which in inspiration swings forward about the great incisura as an axis (4). A lobe adherent to the chest wall or to its fellow is less efficiently emptied

and is more readily subject to reinfection. The mucus tube may actually keep infected material in contact with the tissue and favor inflammation. The mucus tube is perpetually extruded and renewed. With its enmeshed burden of dust, bacteria and debris it is pulled from the trachea into the pharynx and swallowed with each deglutitory act. Extrusion of the mucus sheet is also fostered by a constant slow peristaltic movement which may be observed under the fluoroscope or cinematographically. In addition a swift ciliary motion assists the progress of the mucus tube. Hilding (5) thinks that interruption of the ciliary movement is a major factor in mucus retention.

By whatever failure of the mechanism responsible, interruption of the passage of the great mucus sheet is evidenced by a thickening or inspissation of the mucus at a damaged area. Later coming mucus is joined to the stagnant dried mucus and may obstruct the tubules to such an extent as to produce atelectasis which stops additional desiccation. Nummular masses form which are extruded either by increased activity of the propulsive mechanisms or by increased production of mucus. Irritation of the bronchi at sensitive points induces cough so that a huge draft of air is inspired and expelled against the nummules in expiration with an open larynx. Most sensitive of these points is the carina or bifurcation of the trachea. The mucus may be so tenacious in some cases of whooping cough in infants that frequent aspiration with a catheter may be necessary to prevent asphyxia. Anything which reduces the customary traction of the mucus sheet or permits it to become glued to the surface of the bronchi may prove harmful. Drugs which depress the alimentary tract and decrease swallowing or peristalsis are antiexpectorant and those which stimulate intestinal activity usually stimulate bronchial movements and are expectorant. On this account, morphine is contraindicated in the treatment of pneumonias and to be used with great care if expectoration of large nummules occurs. An overdose of morphine may spell subsequent pulmonary retention. The nervous system should be kept alert and irritable in pulmonary infections, and the patients should be encouraged to keep the alimentary tract active by feeding appetizing food. Frequent normal deglutition resulting from mastication is desirable.

The importance of the continuity and traction on the mucus sheets is exemplified by the old observation in diphtheria that when the mucus sheet is interrupted by a laryngeal pseudo-membrane the introduction of a tube always permits the discharge of large quantities of retained mucus and fluid that has not been lifted beyond the break of the mucus sheet.

It is important to consider the relative humidity and its effect on the mucus sheet in the treatment of the inflamed respiratory tract. The passage of moisture unsaturated air over mucus desiccates it. If the sheet is stagnant it may be completely inspissated and dry plaques of mucus may be found attached to incompletely desiccated mucus which either has been kept moist in an occluded bronchus or has been freshly secreted. I observed a woman in her middle fifties with an harassing cough during a bronchopneumonia in which this condition appeared. She had not been relieved by sedatives but in humidity saturated atmosphere the mucus became soft in fourteen hours and the nummules were

expelled by coughing at first and subsequently there was restoration of the mucus sheet. This patient recovered. On occasion autopsy has revealed mucus completely inspissated lining the tracheo-bronchial tree, and once the chink of the glottis was occluded from below with such a dried mucus plaque attached to a gob of mucus. The usual oxygen tent requires the chilling of the entering air before it enters the enclosure. This is desirable in most cases because an optimal relative humidity (R.H. 50) is thus obtained. When there is much mucus and little expectoration this otherwise desirable low relative humidity may be harmful. The usual supply of moisture from small electric or alcohol heated humidifiers frequently results in an arid atmosphere in the tent or cubicle because they produce more heat than evaporation. On this account, at Willard Parker Hospital they have been discarded and live steam is taken from the heating system which is outside the cubicle. Mechanical humidifiers should be used if the patients are oppressed by the heat. In private homes and apartments the superheated hot water which is often supplied from the boiler yields steam when it is released. Oxygen tents should be run without ice when the humidity is to be maintained and any cooling should be by radiation from outside the enclosure which may be accomplished by having the room in which the oxygen tent is run at a sufficiently low temperature.

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## DR. ISRAEL MOSES, SURGEON\*

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It is a fitting tribute to this individual to grant him the title of surgeon, for most of the active years of his short career were dedicated to the task of surgery. His rôles included that of Military Surgeon to the United States Forces in the Mexican War, first surgeon on the staff of the then recently incorporated Jews' Hospital, New York City, surgeon to the United States Volunteers in the War of the States, surgeon again in civil practice to the end of his abbreviated days.

His life was essentially a public one, dedicated to others, to the relief of suffering, to the aid of the wounded and the ill; a selfless, altruistic career. A fighting but a kindly man, cultured, educated and sensitive, he spent most of his life in army camps and in public institutions with a longing that was evident in his letters and correspondence, for the happiness of a family life, never fully to be achieved.

In the year of his birth, in New York City, in 1823, the family name of Moses had already been well established for probity and for public acts, both in that City and in Philadelphia. His illustrious grandfather, Isaac Moses, had immigrated from Germany, in 1742, settling first in New York and marrying there his cousin, Reyna Levy. Resenting the intrusion of the British during the Revolutionary War, he, with other patriotic Jews, fled to Philadelphia, to which the seat of government had been removed. Some time later he returned to New York to spend the latter part of his useful life as a prominent citizen, respected in his home, honored for the active rôle he had played and was playing in national and communal affairs.

The quiet but highly patriotic efforts of Isaac Moses during the period of the Revolutionary War have received but insufficient attention and recognition. He was a partner of Robert Morris, a member of the militia who advanced to the United States 20,000 pounds in Specie in exchange for Continental dollars to finance the Canada Expedition, for which he among others was thanked by John Hancock. The energy and capability of this man are seen in his many public accomplishments. He helped raise funds for instituting the first Fire Department in Philadelphia; his efforts helped institute the first Bank of the United

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† Personal data in reference to Isaac, Joshua and Israel Moses was obtained by referring to the publications of the American Jewish Historical Society, Volumes 21 to 28, and from correspondence and papers turned over by Miss Blanche Moses to the Library of Columbia University.

Data relating to the military career of Dr. Israel Moses was obtained directly from the War Department and the records of the Civil War.

States; through his appeal to the State Legislature in behalf of fifty merchants of Philadelphia and New York, the first Custom House was established in the latter city. He was honorary Colonel of the Militia during the Revolutionary War; and founder and member for thirty years of the New York Chamber of Commerce. Benjamin Franklin referred to him as "my friend of austere culture and true knowledge," a tribute of veritable merit from the tongue of that most wise of men and most frank of critics.



Dr. Israel Moses

Apparently his son Joshua carried on the tradition of the Moses family as honorable merchants and as men of affairs. The existence of an embossed invitation and card of admission to the coronation of the Emperor Napoleon I in Paris, bespeaks his recognition as an individual. He proved a citizen of great value; he helped to mold the true principles of international affairs in London, Paris, Ghent and Geneva. In such a capacity he was representing Governor de Witt Clinton and the State and the City of New York. He was present at the negotiations leading to the signing of the Treaty of Ghent.

Thus, Israel Moses, one of the seven sons of Joshua Moses, entered life in 1823

with the heritage of a good name, the scion of a family of recognized culture and fortune.

The school days of Israel Moses seem to have been those of any boy born and bred in the metropolis; but on the day of his graduation from Columbia College as a Bachelor of Arts (1841) he was awarded two medals, one for "proficiency in Latin," and one for "merit in English." His diploma as a Master of Arts followed after three years. During that period he was undoubtedly serving under the preceptorship of a recognized practitioner of medicine, for in 1845 he received his degree of Doctor of Medicine from the College of Physicians and Surgeons, an engraved diploma of exceptional elegance, bearing among others the signature of the illustrious Dr. Valentine Mott.

His internship at the New York Hospital probably represented as fine a practical course of training as was afforded anywhere in this country, for that institution, founded in 1767, one of the three existing hospitals in the metropolitan area, represented then as it does now a standard of unexcelled scientific merit.

That very year saw the outbreak of the war against Mexico; in fact, within a month of the day upon which his two diplomas had been granted as a graduate intern, the battles of Palo Alto and Resaca de la Palma were being fought (May, 1846).

The spirit and the strength of his forbears seemed to inspire the maturing physician; rather than enter civilian practice in a time of national crisis, he elected to serve in the minute corps that represented the nucleus of the medical department of the small standing army of that day. Appointed surgeon, January 18, 1847, he served with the army of occupation (Vera Cruz and Toluca, Mexico) from July, 1847 to September, 1848.

Let no one underestimate the severity of the fighting against Santa Anna and his Mexican auxiliaries. The annals of the military history of that war speak of most bitter and stubborn defense and of most valiant and rash attack. As an instance, there is described in the reports of the Medical Corps of our Army, accounts of two occasions in which during gallant attacks superior officers were sacrificed. On each occasion the surgeon of the regiment, relinquishing his scalpel, rallied the infantrymen and presumably led them to overwhelm the enemy, at the cost of his own life. Perhaps incidents such as these were the dominant motive in the later life of Israel Moses to inspire him to make in the early years of the War of the Rebellion a most unusual decision.

After the signing of the peace concluding the Mexican War, his services with the Army continued. His regiments covered a wide range of territory including such far-flung encampments as Wisconsin, Fort Leavenworth, Missouri, with a Rifle Regiment and with the First Artillery in Oregon, and the then Washington Territories as well as in Texas. His application for sick leave was granted in 1855 and was soon followed by his resignation because of ill health.

The City of New York, in 1855, was reputed to number about 510,000 souls; included in this census were 25,000 to 30,000 Jews, constituting a rapidly growing, respectable, and prosperous nucleus within the community. But not all were prosperous, for the abortive revolutionary outbreaks in Europe in 1848 had initiated a wave of immigration to the freer soil of the New World; in this wave of

immigration were included many of the *intelligensia* of Germany, worthy but impoverished by their trek. The large and growing metropolitan city, for its size and population, was as yet poorly provided with hospitals. The dread of the medieval Hotel Dieu still overhung institutions for the care of the sick; bacteriology, biochemistry, and the scientific approach to healing were vague concepts, and aseptic surgery had not yet been conceived.

Old Bellevue Hospital, founded in 1736, had already served the masses for well over a hundred years, as had also the New York Hospital, the prototype of the private hospital of its day, with its chosen staff and meticulous careful efficiency.

The need for new hospitals for the growing city became apparent at the turn of the half century; one notes the foundation of St. Vincent's Hospital (1849), a sectarian institution, and of St. Luke's Hospital (1850), based similarly on a selected creed. To Sampson Simson and his co-workers is credited the foundation of the Jews' Hospital, in 1852, a small building housing 45 beds for the care of the sick; simple and unassuming in design and conception, sectarian too, in basis, as were all but the public city hospitals of that day. Medical and surgical beds and wards were not yet divided, the specialties in practice not yet recognized. Soon after the doors of the Jews' Hospital had been opened to receive the sick, Dr. Israel Moses, Surgeon, recently retired from the United States Army Medical Corps, was appointed an Attending Surgeon to that institution.

The very first case admitted to the new hospital was one of fistula-in-ano, operated successfully, and so recorded by Dr. I. Moses, Surgeon. From that date to the outbreak of the Civil War the surgical achievements of Moses are written into the records and books of that office, operations covering every field of the human anatomy from infections to hernia, from trephining to amputation. In the fine, Spencerian script of the recording clerk are noted the successes and the failures and the fine efforts of the former Army man attempting to convert his practical experience on the field to the needs of the civilian population.

The monotonous round of daily chores seemed apparently undisturbed by the dark clouds gathering below the Potomac. But probably not unnoticed by such a vigilant and alert mind as that of Moses. The clarion call for volunteers enunciated by his President, Abraham Lincoln, results in a stern purpose and in a resolute decision of unusual nature.

Incredible as it may seem to us, with our conception of highly specialized functions allocated in times of national emergency, Dr. Moses answers this call for freemen and is mustered in, not as a surgeon, not in his capacity of a medical man or health officer, but on July 23, 1862, as Lieutenant Colonel, second in command, of the Third Regiment, Excelsior, or Sickle's Brigade, of the United States Army, a fighting man, stationed at Camp Scott, Staten Island. At the age of 38, Lt. Col. Moses is whipping into shape a regiment of raw recruits gathered from New York City, from various sections of the State, and some few companies from neighboring New Jersey. Nor is he alone of his family represented in the Federal Service, for his older brother Isaac is also enrolled as Major and as Assistant Adjutant General in the United States Volunteers.

The summer heat of New York Bay is already forgotten in the shivering blasts

and wet mists that cover the camp on the Potomac, fifty miles below Washington. The regiment is being trained as part of Hooker's Division of the Army of the Potomac. McClellan is a stern disciplinarian, the enemy is in strength, and the stigma of Bull Run must be erased.

"The cold wind is howling a melancholy wintry song through the somber pines," lines in a letter to his sister-in-law words that bespeak a literary culture, a clarity of expression, and a human gentleness that would still seem to warrant the award of "merit in English" that accompanied his graduation from Columbia several years ago.

Four months later the regiment is still encamped; his bookcase, for he must have a bookcase, is a biscuit box turned upside down; his library consists of twenty or more books of a decidedly warlike character. An empty gun-chest serves as a chair; he reads himself to sleep every night by candle light. His diet includes pork and beans at least five times a week, which he deliberately says he eats with good appetite. No complaint of a monotonous fare which one can easily assume was quite foreign to his childhood home. Years in the army have carried him far from his sheltered and educated boyhood, but the old memories and tendernesses are still there, for his letters to his sister-in-law and family are always affectionate and beautiful. "I am so in the habit of writing my name as above (I. Moses, Lt. Col.) that I have unconsciously done so. I have almost forgotten the M. D.; though I occasionally perform a surgical operation and prescribe for the sick, I don't attend any ladies!"

The March winds are stirring; there is every sign of an onward movement. The Rebels have suddenly retreated overnight; freshly killed beef, guns, artillery deserted. We are victorious everywhere. But the canny experienced Moses does not think the war is at an end yet. He predicts a terrible conflict. "There is no doubt that they are much demoralized and panic stricken, but a fortunate turn may reanimate them and prolong the struggle."

From Williamsburg, Virginia, they are "on to Richmond", and the Peninsula Campaign is in full swing. The natural optimism of the wonderful Army of the Potomac is reflected in the letters and buoyant spirits of the ever cheerful Moses. The Rebels were licked; some thought they would stop nine miles in front of Richmond, others thought they would retreat into the Cotton States. "I suppose we shall be in Richmond in a few days," a prophetic utterance that breathed none of the disappointment to come.

Shortly he speaks of being wounded, but of paying little heed to his injury of the previous day. Eventually this hardy, self-denying optimist became curious. "My wound turned out to be a buckshot which furrowed my back, but I did not have time to examine it until yesterday, when becoming troublesome and inflamed from riding, I looked and discovered its nature." From which incident one draws the inference that the intrepid Lieutenant Colonel, in the enthusiasm of his leadership, paid scant attention to his own physical well-being, injured as he was by this time to the hardships of camp and field; and that the valiant rebels were still armed in part at least with shotgun and buckshot!

The campaign must have been a hard one, for at one time he speaks of still having 800 men capable of serving in the field, but the implication of serious

losses is evident. The retreat down the James River, and the disappointment over the outcome of the campaign seemed to have left a tone of embitterment and frustration. The transfer of Colonel Nelson Taylor, the Commanding Officer, to another Brigade, and his replacement by a stranger, seemed to have a determining influence in the next step of his career. For in October of that same year, 1862, Lieutenant Colonel Moses of the Third Excelsior Brigade, becomes Dr. I. Moses, Surgeon of Volunteers stationed at Finley Hospital, Washington, D. C. In so doing, Dr. Moses, like all professional persons, particularly those bred in medicine and surgery, reverts to type. Other surgeons before had exchanged the scalpel for the sword; others would do so again. For later, at the outbreak of the first World War, many British surgeons volunteered and served as active combatants and machine gunners; this to so great an extent that the mortality among them in the embattled fields of Flanders created a great dearth and scarcity of English physicians and surgeons.

In the Federal Forces in 1862, medical preparedness was notoriously deficient. The chaotic conditions, the lack of organization, of personnel and of Sanitary supplies created a situation which the nation realized, but which the old guard Medical Department was unwilling to admit and incapable of recognizing. The creation of the United States Sanitary Commission, as the result of noble efforts and of voluntary contributions by high-minded citizens, helped greatly to save a pitiable situation in which the wounded and sick were inadequately helped, transported and carried in primitive vehicles, with medical supplies and the very necessities of the seriously injured often lacking and inordinately delayed.

After the Peninsula Campaign, the lack of true efficiency in the Medical Department of the Army was more fully recognized than ever. The improvised and rudimentary ambulances utilized by the Sanitary Commission, and the passenger vessels hired in the emergency to transfer the wounded crowded on the decks of these vessels, exposed to rain and hunger, these all did not do more than point to the need for complete reorganization.

It is therefore not strange that at this time Moses heeds the call of the administration for more and more doctors for the rapidly growing forces of combat. The sight of suffering arouses in him the old longing to help the sick and tend the injured; the smell of chloroform, the slipping displaced bandages, recall the field emergencies of the Mexican War, bringing again to memory the ordered system of his intern days and of the years of service in the operating room of the well equipped Jews' Hospital. The precepts of Hippocrates, residual in the blood and mind of every trained medical man, rise with the sight and hearing of anguish, and the physician becomes himself again.<sup>1</sup>

The scene of activities now shifts to Eastern Tennessee. The warring days of late December, 1862, saw the Army of the Cumberland, under Rosencrans, facing before Murfreesboro the gray, tattered Army of the Tennessee under the

<sup>1</sup> It is interesting to observe that at least two members of the Attending Staff of the Jews' Hospital were serving a public function. Dr. A. Jacobi and Dr. E. Krackowitzer were acting as Special Inspectors of the United States Sanitary Commission in 1863 and 1864.

Fabian Bragg. Both armies lay in the trenches in the rain, in the coldest winter nights of many a year. Supplies were late in coming; the improvised shelters of the Sanitary Commission, however, were well stocked. The battle, a stubbornly fought contest, extended over the last days of the month; New Year's day was rainy and colder and the wounded were rapidly overcrowding the scant facilities in the field. Bragg was, if anything, victorious, but he did not realize that fact. He had fought a good fight, strategically well thought out, but his army was cold and hungry and tired. He called a council of his generals, who advised retreat to Chattanooga. The field of battle and the town of Murfreesboro were evacuated to the Federal forces; the Federal wounded were rapidly congregated in eight improvised hospitals, in churches, in farm houses and hotels; order was rapidly appearing out of chaos in the intelligent hands of Dr. I. Moses, Medical Director at Murfreesboro, Tennessee.

Many months of recuperation and rest were to elapse before the spring advance against Bragg was to be resumed. Wounds were to be dressed and healed, operations to be performed, the general health and sanitation of the Army to be revised and renewed, convalescents to be nursed back to health, endemics and epidemics to be stamped out. "The sick are provided with every luxury and complaints are seldom if ever made. Dr. Moses, the Director of the Post, makes it his business to inquire into all the details of the hospital from the office and ward to the culinary department." At the request of the Medical Director, permission is received to quarter convalescents on the farms of the surrounding country. This has the double advantage in that the soldier receives pure and wholesome food, plenty of fresh air and freedom to exercise, and is rapidly returned to his regiment, his place being filled by another invalid.

During the cold weather, Dr. Moses with his usual foresight and thoughtfulness for the comfort of the sick and wounded, had all the ice-houses in the post filled to their utmost capacity with a good quality of ice. A perusal of the surgical reports of the Army shows to what extent fresh cold water was utilized as the routine dressing of wounds and injuries.

Another hobby of the Medical Director is to institute gardens and tilled areas wherein the convalescents may work and live and raise fresh vegetables for the boys in the hospital.

Sprue had long been an enemy of Dr. Moses; every thought and act of the Medical Director seemed to anticipate or realize the need for the best of hygienic surroundings and the exquisite consciousness of the spiritual and moral well being of his wounded charges. In spite of the business of the camp, and the directorship of the eight hospitals, Moses, the capable and experienced surgeon, has been at the operating table, for the surgical records of the War of the Rebellion contain innumerable case-histories composed by the indefatigable surgeon. Cases range over every type of gunshot and bayonet wound; the records are in many instances brief, but well kept, and the episodes followed-up, where possible. In the long evenings the tireless physician is conscious of the scientific necessity of filing and reporting his operations in current medical literature.

Already in 1864, the American Journal of the Medical Sciences published a

paper entitled "Surgical Notes of Cases of Gunshot Injuries Occurring During the Advance of the Army of the Cumberland in the Spring of 1863," by Dr. I. Moses. Every type of gunshot wound of face, head, extremities, body cavities, is amply covered with sketchy but intelligent details and remarks. The results are often surprisingly good, conservative treatment is encouraged at all times. Throughout his writings one notes the anxious care of the Director for the general health and welfare of his children, the emphasis upon the bedding and the clothing and the fresh food, and the welcome warm sunshine.

He is discouraged over the course of bullet wounds of the skull or cranium. They are almost universally fatal; in his experience in this and in former campaigns it makes little difference whether one trephined, removes the depressed bone, or let them alone. Even the seemingly trivial cases, after a longer or a shorter interval, with few exceptions, follow a fatal termination. But a few exceptions to this dismal rule preserve a modicum of optimism; his results are no worse than those of the celebrated Stromeyer in the hospitals of Vienna, London and Paris, and probably better than those encountered in the depressing experiences of the English and French surgeons during the Crimean Campaign.

Dr. Moses has an aversion to amputation, except in urgently clear indications on the field of battle. In the more quiet atmosphere of his base hospitals his natural scientific logic and his innate conservatism come to the fore. He has saved three out of four cases of gunshot wound of the upper extremities without amputation; all the wounds of the forearm and hand recovered without sacrifice of the limb.

For the first time he publishes his views on the conservative treatment of gunshot wounds of the knee. He criticizes the disappointing results from amputation; he puts in a clarion call for open incisions and free drainage and encourages a more conservative and preventive course aimed at saving a functioning extremity. He is becoming an outstanding exponent of this type of conservative approach to knee injuries; his comments are widely read and widely quoted in the European literature for he has saved, to the best of his knowledge, five out of ten gunshot wounds of the knee, the largest single joint in the body and the one notoriously subject to fatal infection.

Of injuries to the ankle and the foot he writes, "I have been greatly delighted at the results of several of our cases where I was in great doubt whether they could be saved, and have turned away unresolved what to do. I have more than once been the only opposing voice to amputation and have rarely, if ever, had reason to regret my decision."

The long inactive spring of 1863 has passed; the Army of the Cumberland is again on the march, Bragg has been outwitted and outflanked, and has by necessity evacuated the small city of Chattanooga and gathered his forces in the hills and impregnable mountains south of the Tennessee River. In September, Moses receives his orders to take charge of the hospitals and medical facilities freed by their retreat. He is Surgeon-in-Chief of the General Hospital and Medical Director of the Post of Chattanooga. He will take charge of that host of wounded and injured, derelicts and broken men that will be gathered

to him during the succeeding three months of bitterly contested battles in the passes and on the slopes of Chickamauga, of Lookout Mountain, and of Missionary Ridge.

The rebels had destroyed much of value in their retreat. Hospitals had to be reconstructed out of nothing, bedding and supplies and ward necessities improvised while the city itself was often under shell fire. The early disastrous defeat of the Army of the Cumberland was only at the last moment retrieved by General Thomas, the "Rock of Chickamauga." The wounded piled in by every type of conveyance, the battles were of the most sanguinary nature.

In the first few days of September the Union losses were well over 13,000 men and officers killed and wounded. Up to the first of November, Moses alone diligently recorded and catalogued 1,904 cases of variously seriously wounded individuals, all of whom were housed and cared for, and many of whom were actually and personally operated upon by himself. Thanks to the liberality and efficiency of the Sanitary Commission, little was wanting for the care of the injured; though rations were seriously reduced during the siege of the city, though the hospitals and wounded had often to be evacuated to the rear because of the constant threat and actuality of shellfire during the siege of Chattanooga, fresh bread was never lacking and every provision, even with reduced supplies, was forthcoming. The weather was cold, wet and depressing, blankets were hung in the empty windows and doorways, luxuries and fresh food were at a premium. Moses is a great advocate of canned milk, and canned soups and beef essence, most of which could still be supplied in quantity by the Sanitary Commission. It is interesting to note that just as this Civil War is the first conflict to be photographed, so also is it probably the first war in which canned and preserved foods were utilized.

Notwithstanding all the tumult of battle and its associated confusion, Moses has still found time to tabulate, and scientifically to analyze his surgical material and report his results. For already in October, 1864, the second article appears from his pen, again published in the very exclusive *American Journal of the Medical Sciences*, entitled "Surgical Notes on Gunshot Injuries."

All of his cases are catalogued and classified; he studies them with critical analysis and rare surgical discrimination. Four cases of tetanus (lockjaw) constitute the basis for a dissertation on that subject, a thesis which even before the discovery of bacteriology and the bacterial nature of the disease, is scholarly and discreet. He discusses with great intelligence gunshot wounds of the lungs, the incidence of hemorrhage on the battlefield and in the subsequent course, the technique of the ligation of arteries. He seems familiar with the experiences of European surgeons and quotes freely from their opinions.

Gunshot wounds of the knee had previously been the object of his most rapt attention. He approaches the subject again, but now with much more timidity than he did a few months before. Two of the five cases which he had previously reported as cured or greatly improved, have since, to his knowledge, succumbed to their wounds. He is frank in his admission and correction of his previous statement, he is scientifically candid and openly sincere and honest. He at-

tributes most of the depressing fatality in the cases of knee wounds to the delay, often of ten to twelve days, in the transportation of the wounded to the field hospital, delay engendered by the swaying lines of battle and the capture and recapture of fixed positions in ever changing lines of advance and retreat.

Moses serves with the active forces of the Army in the field until April, 1864. Probably on account of ill health he was relieved, but continued on duty with the Provost Marshall General until October, 1864. For the remaining period of the Civil War he is less arduously employed in examining recruits in New York City. On July 24, 1865, he is mustered out after having received the brevet of Lieutenant Colonel for faithful and meritorious services during the war.

The remaining years of his life are few and are spent in Philadelphia. His health was not good; it is not known whether he practiced medicine and surgery during this period. He died in 1870 at the relatively early age of forty-seven.

Of his character and private life we read, between the lines of the letters to his family, sentiments of devotion, a high sense of fidelity and of love of those whom he had rarely the privilege of seeing. The opportunity of enjoying with them the luxury and warmth of close familial contact was never realized. He remained a bachelor, yet like most men deprived of contact with his beloved ones, he breathed for them hearty affection and at all times solicitude for their welfare. Always modest and self-effacing, he typifies the gentleman of culture and education, a man of rare discrimination and judgment in matters scientific and surgical, and in subjects relating to martial experience.

As a soldier he is a natural born leader, hard working, efficient and reliable. Most of his active life is spent in hospitals and camps. As an offspring of the illustrious family of Moses, he represents the best type of literary and cultural Jew, one who served his country without stint, who gave to the national welfare his greatest effort.

He had the unique distinction of having been the first surgeon to the relatively recently established Jews' Hospital in New York. Had he retained and utilized this opportunity he might have grown prosperous and renowned in the rapidly growing community of that metropolitan city. His greatest effort, the most concentrated strivings of his mature years, he devoted to the service of this nation's welfare in times of warfare and crisis. His family, his nation, and The Mount Sinai Hospital may well point, in times of National crisis such as exist at present, to the career of Israel Moses as one of outstanding accomplishment, as one of altruistic devotion to the cause of civilization and democracy, a man of Maccabean fortitude.

IN RETROSPECT  
AND ALSO LOOKING BACK AT THE MEANING OF SOME ILLUSTRATIONS IN OLD  
MEDICAL BOOKS

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It affords me great pleasure to contribute a short paper to the volume published in honor of Dr. Alfred Meyer in his ninetieth year. This allows me to express to him my affection and my admiration of his sterling character. His fearlessness and readiness at all times to speak for what he considers just and right, has made an impression on all of us no matter whether we have known him for a few or for many years.

It has been given to few physicians to live through so many great events in the history of medicine. Just think of it! To have graduated in medicine in 1877, a few years after blood smears had been introduced by Ehrlich, and to have been in practice when the typhoid bacillus (1880), the tubercle bacillus (1882) and the diphtheria organism (1883) were discovered! And to have witnessed the birth of our knowledge of antiseptics and asepsis, of antitoxins, the Roentgen ray and radium, of salvarsan and the Wassermann reaction! And to have been in medicine during the great advances in general surgery and the splitting off from general surgery of the surgical specialties such as otology and neurological surgery! What a grand panorama has been spread before Dr. Meyer's eyes!

In joining with others to honor this old friend, it seemed to the writer that it might not be inappropriate to jot down a few notes regarding some other friends, old medical books. Old books should be the friends of everyone, and old medical books should be the friends of every physician. "When you range back and forth through the centuries, when you weigh the utterance of some great thinker, or absorb the meaning of some great composition in painting or music or poetry, when you live these things within yourself and measure yourself against them—only then do you become an initiate in the world of the free." In making this statement in an address at Duke University, Mr. Willkie had the humanities in mind, but I am sure that the same observation is applicable to the broadening effect upon the physician of studies of old medical books.

If old medical books are properly tasted and digested, they will be found to be not dry and uninteresting but full of life. And illustrations in old medical books will often tell an interesting story of the development of different branches of our healing art.

In the early days of anatomical illustration, the artists made free hand drawings and, not so rarely, anatomical correctness was sacrificed to the artistic taste of the draughtsman. The artist desired, above all, to make a pleasing picture, and with this end in view, anatomical details were often surrendered. This is shown, for example, in the drawings illustrating the brain in the "De Dissectione"

of Charles Estienne (Stephanus) published in 1545, and to some degree even in the remarkable drawings of Stephen Calcar for the "Fabrica" of Vesalius. Some of the drawings by Estienne, intended to illustrate the anatomy of the brain, are reproduced in figures 1 to 4.

In figure 1, the surface of the cranial dura has been exposed by removal of the skull cap. Note that the figure of the man and the landscape dominate the picture. The skull cap is hung on the branch of a tree under a cloudless sky. In figure 2, the dura has been divided and reflected and the brain is exposed. Note that *now* the individual is seated, the skull cap lies on the table, the branch of the tree is broken and clouds are appearing in what was a cloudless sky. In figure 3, the brain has been sectioned and the ventricles and other intracerebral structures exposed. The individual is now so much affected that he has fallen over the table. Dark storm clouds are appearing in the heavens. In the fourth figure, the brain has been entirely removed, showing the interior of the base of the skull. So advanced is the dissection, that the prone position of the individual indicates that the maximum injury has been inflicted. This is shown, also, by the ruined buildings in the background and the broken tree trunk. The artistic effect produced by these four illustrations is certainly striking, and the message that was intended to be conveyed, of the increasing difficulty and complications of the dissection, is clear, but the rendering of the anatomical portion, i.e., the anatomy of the brain, is small and indistinct.

As I have already mentioned, one can often gain a knowledge of the development of some branch of medicine from the illustrations in a series of old medical books of successive periods. For example, the advances in our knowledge of human anatomy by dissections of the cadaver, are demonstrated by the title page plates in a few early medical works. It is well known that up to the time of Mundinus (in the thirteenth to fourteenth century) dissection of the human body was considered a sacrilege, and much if not most of the knowledge of human anatomy was gained from the dissection of apes and swine. Most of the anatomy of Galen was based upon dissections of animals, and because Galen's writings were for almost one thousand years the Medical Bible, many of the anatomical errors made by Galen were copied by succeeding generations of anatomists.

Figure 5 is the plate from the title page of a book on Anatomy by Mundinus which was completed in 1316 but was published more than 150 years later. The copy from which figure 5 is taken was published in 1493. The "Anathomia" of Mundinus was really a dissecting manual and was full of Galenic errors, but it was almost the only textbook of anatomy based upon the dissection of human bodies, for almost one hundred years. The figure shows the "professor" seated in a pulpit chair and expounding Galen from the book on his lap. The professor did not dream of soiling his fingers by handling the cadaver but his barber servant is doing the dissection and handling the viscera.

Figure 6 is the plate from the title page of the anatomy of Mundinus published in the "Fasciculus Medecinae" of John of Ketham in 1497. The fasciculus was a collection of medical writings for the physicians of those days. The illustra-



FIG. 1. The anatomy of the brain from *De Dissectione* (Stephanus), 1545. (Compare with figs. 2, 3 and 4.)



FIG. 2. The anatomy of the brain from Stephanus. The dura has been opened showing the brain.



FIG. 3. The anatomy of the brain from Stephanus. The brain has been partly removed to show the ventricles and other intracerebral structures.

tion again shows the professor seated on a dais and reading from Galen, while the dissection is being done by a servant, but *now* there are students and perhaps a demonstrator (the figure in the lower right foreground).

In figure 7, the "professor" is still seen seated and commenting from Galen, but there is now an instructor who indicates to the dissector where the incisions should be made, while the attention of the students is divided between the "professor" and the dissection. This illustration is a photograph of the plate on the title page of the "Isagoge Breves" of Jacobus Berengarius of Carpi, which was an anatomical compendium first published in 1522. The plate shown in figure 7 appeared first in the 1535 edition of Berengarius.



FIG. 4. The anatomy of the brain from Stephanus. The brain has been removed to show the base of the skull. This is the last of the four illustrations. The body is prone. The catastrophe is indicated by the broken tree and the ruined building in the background.

Figure 8 is the celebrated plate from the title page of the first edition of the famous "Fabrica" of Andreas Vesalius published in 1543. Vesalius was the founder of modern anatomy, and his teachings based upon dissections of human cadavers overthrew much of the work of Galen. Figure 8 shows that *now* conditions are entirely changed. No longer is the professor seated and commenting from Galen while dissection and demonstration are done by others. Vesalius is at the dissecting table himself, *he* is doing the dissecting and demonstrating on the actual cadaver. The only reference that he will make will be to bones of the body and for this purpose he has an articulated human skeleton near the dissecting table.

These four figures tell the story of the development of dissection of the human



FIG. 5. Title page from the *Anathomia* of Mundinus, 1493, showing the "professor" and the dissector.



FIG. 6. Title page from the anatomy of Mundinus, published in the *Fasciculus Medecinae* of John of Ketham, 1497, showing the "professor," dissector and students. The plate was colored by an unknown artist.

**Anatomia Carpi.**

**ISAGOGE BREVES**

Perlucide ac uberime, in Anatomiam hu/  
mani corporis, a, cōmuni Medicorum  
Academia, usitatam, a, Carpo in Al/  
mo Bononiensi Gymnasio Ord/  
nariam Chirurgiæ publicæ  
Docente, ad suorum  
Scholasticorum  
preces in lucē  
date.



VENETIIS ANNO .D. M.CCCCC.XXXV.

*Dionysij faballi*

FIG. 7. Title page from the anatomy of Berengarius, 1535, showing the "professor," demonstrator, dissector and students. As in figs. 5 and 6, the professor will not soil his hands by touching the cadaver and he is still reading what Galen says.



B A S I L E A E.

FIG. 8. Title page from *De Fabrica Humani Corporis* of Vesalius, first edition, 1543. Vesalius himself is in the amphitheater doing the dissecting and demonstrating.

body. Although the text of old medical writings will often make both interesting and instructive reading, the study of the often crude illustrations will give us an inkling of the advances in anatomical knowledge that were being made. Therefore, the student of old medical books should never look at the illustrations as crudities and curiosities which merit only a passing glance. He should ponder their meaning and should meditate on the state of knowledge which they indicate. Then, in mind, we are transported back to the period when modern human anatomy emerged from the ignorance and superstitions of the Dark Ages! When studied from this point of view, are not these old illustrations full of life?

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## METASTATIC BRAIN TUMOR WITH BRONCHOGENIC CARCINOMA AS THE PRIMARY SOURCE

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In a previous communication (1) it was pointed out that observations on the anatomy and clinical manifestations of metastatic brain tumor did not keep pace with the constantly growing abundance of data pertaining to tumors primary in the brain. This situation still exists in spite of the fact that the metastatic intracranial tumors are not at all rare as several available statistical studies indicate. Some of these statistics estimate the incidence of metastatic brain neoplasm among verified brain tumors to be as high as 10 per cent (Dandy (2)), while the more carefully investigated material yields a percentage ranging from 4.2 per cent (Cushing (3)), 6.4 per cent (Walshe (4)), and 13.5 per cent for The Mount Sinai Hospital collection of brain tumors (1). The relatively high incidence in the latter survey was explained by the fact that the material investigated was drawn from the several clinical divisions of the hospital and not only from its neurological and neurosurgical services.

It is obvious then that more comprehensive studies of this type of lesion from both the clinical and anatomical points of view are highly desirable. Such studies are likely to show, as found in the material to be surveyed in this report and as already noted in the previous report (1), that the lungs constitute a most common primary site for malignant neoplasms metastasizing to the brain, and often are an early interceptor of such a lesion.

In the aforementioned report (1) it was shown that in 33 cases of metastatic carcinoma of the brain, autopsy disclosed the primary lesion in the lung in 19 cases. Among these cases, instances were not rare in which the history, clinical observations and even x-ray examination failed to yield a clue as to the primary seat of the malignancy. In some instances the existence of a brain tumor could only be suspected, remaining in doubt until late in the clinical course. In other instances the presence of an expanding lesion in the brain and its neoplastic character were recognized but the metastatic nature of the lesion was not suspected. This was particularly true of cases in which the clinical picture was that of a single isolated expanding lesion.

It was thus felt desirable to survey, both anatomically and clinically, the available cases of metastatic brain tumor in which the primary lesion was found in the lung. These cases fall into two groups: A large group consisting of 18 cases in which the primary focus, as established by complete autopsy, was found in the lung or part of the bronchial tree. In the second group, no biopsies were available and post-mortem studies were limited to the brain, hence the primary source could not be fully ascertained. The only clues of some assistance in these cases

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were those of clinical or roentgenologic character. The histologic character of the tumor itself could not be regarded as sufficiently reliable evidence as to the true site of origin of the primary lesion. So, although this group contains 16 cases, none of them were sufficiently instructive to be included in this study.

In analyzing the group of cases of metastatic brain tumor in which the primary source was discovered in the lung by complete post-mortem examination, it was found convenient to divide it into several subgroups: Subgroup A, consisting of cases in which no pulmonary signs or symptoms were recognized at any time either preceding or concomitant with the development of cerebral manifestations; subgroup B, consisting of cases in which no recognizable pulmonary symptoms or signs were present at any time preceding the development of cerebral manifestations, but in which clinical evidence of pulmonary neoplasm or a similar focal expanding lesion was found following the development of signs and symptoms of cerebral dysfunction; subgroup C, consisting of cases in which signs and symptoms pointing to probable or definite pulmonary involvement but unconfirmed by x-ray examination preceded or became manifest in the course of the development of cerebral disturbance; subgroup D, consisting of cases in which signs and symptoms of pulmonary involvement, confirmed by x-ray examination of the chest, preceded or were disclosed in the course of the development of manifestations of cerebral involvement.

#### ILLUSTRATIVE CASES

*Subgroup A.* This consists of only two cases. In neither did the past history of the patient disclose any signs of pulmonary affliction nor did these patients reveal any sign of pulmonary involvement while they were being observed for their cerebral manifestations. The discovery of the metastatic character of the tumor in the brain by biopsy in one instance was quite unexpected, but the disclosure at post-mortem examination of the primary focus of the lesion in the lung came as a total surprise.

*Case 1. No signs or symptoms of pulmonary involvement throughout the entire clinical course; acute onset of cerebral manifestations characterized by emotional instability, carelessness in personal habits and some intellectual depreciation; meager focal signs; right frontal lobe tumor diagnosed; craniotomy; removal of tumor; gradual recovery interrupted by sudden and rapid decline with the development of bilateral external rectus palsy. Death; necropsy; area of disintegration at the site of the removed tumor; metastatic tumor in the left frontal lobe and another in the pons.*

*History:* (Adm. 499833; P.M. 12388). S. K., a man, aged 49 years, three weeks before consulting me began to display mental changes, characterized by alternating periods of facetiousness and tearfulness. He began to make many errors in simple calculation and exhibited indifference to infarctions of social amenities, urinating and soiling his clothes often in the presence of others without manifesting physical or emotional discomfort. In view of these mental changes and the few neurological signs, such as mild left facial weakness and slightly elevated deep reflexes on the left side, a provisional diagnosis of a right frontal lobe neoplasm was made. He was referred to the hospital for observation and ultimate surgical intervention.

*Examination:* The patient was found to be constantly grinning and engaged in making silly drawings. He was poorly oriented for time and place and would frequently confabulate to make up for his defective memory. He exhibited a left central facial weakness, slight deviation of the tongue to the left; left Hoffman sign with slight increase of the deep reflexes in the left upper extremity. There was a suggestive left Babinski sign and a left grasp reflex.

*Laboratory Data:* The cerebrospinal fluid was negative in all phases except for a 4 plus Pandy reaction and a total protein of 87 mg. per cent. An electroencephalogram was interpreted as indicating the presence of a midline frontal lesion, possibly expanding. *X-ray examination of the lungs showed no abnormality.*

*Course:* The presence of a right frontal lobe tumor was regarded as fairly certain in the absence of evidence of a primary lesion elsewhere and a craniotomy was performed without further delay. A tumor was removed from the right frontal lobe. The patient made a fairly satisfactory, though slow, recovery from the operation and left the hospital with only minor residual mental changes.

*Surgical Pathology:* The surgical specimen was diagnosed as metastatic carcinoma, primary focus undetermined.

*Terminal Course:* Following the patient's return home his condition remained unchanged for a few weeks. Shortly thereafter he began to show evidence of advancing mental disintegration. He became silly, snatched toys from the hands of his child and played with them himself. What was still more striking was that he began to butt into objects on either side of him, as though his vision was defective. Examination disclosed that his eyes were in fixed convergence, and that he was unable to rotate each eye into the corresponding lateral canthus. Obviously there was bilateral paralysis of the external recti.

He re-entered the hospital where he gradually disintegrated mentally, passed into stupor and died nine months after the onset of signs pointing to cerebral involvement.

*Necropsy Findings. General:* Small primary squamous cell carcinoma, upper lobe of the left lung; chronic and acute purulent bronchitis; emphysema and edema of the lung; parenchymatous degeneration of the myocardium; atherosclerosis of the aorta.

*Brain:* A brownish discoloration was found over the dorsal and orbital surface of the right frontal lobe. In the left frontal pole there was a walnut-size cyst which collapsed in the process of removal of the brain with an escape of serous fluid. On sectioning the brain the left hemisphere was found to be larger than the right and contained in its central portion a well circumscribed tumor which had a hemorrhagic center and a pearly white periphery. In the region of the right frontal pole there was a cyst-like defect, the site of the previously removed tumor. In the region of the pons, directly underneath the fourth ventricle there was another large well circumscribed tumor mass (fig. 1). It almost completely compressed the fourth ventricle.

*Microscopic Observations:* Section through the tumor mass stained with hematoxylin and eosin displayed a well circumscribed metastatic neoplasm, its cell form being epithelial in character, of a tall columnar variety, arranged in acinar fashion, usually containing a vascular core. There also were large areas of necrosis and hemorrhage.

*Comment:* Of significance in this case was the absence of any pulmonary signs pointing to the primary site of the lesion. In view of the abrupt onset, the metastatic character of the lesion was not entirely ignored, and search was made for a primary focus of malignancy in the chest; none was found and in its absence craniotomy was justifiably undertaken. Even were the lesion unquestionably established as metastatic, craniotomy would still have been indicated for, as shown in a previous communication (1), there are exceptional instances of solitary metastatic lesions which lend themselves to surgical intervention. This is particularly true in a case in which localization is readily established. Not

without interest was the discovery of the pontine tumor compromising both nuclei of the abducens nerve.

*Case 2. No signs of pulmonary involvement; acute onset of cerebral manifestations of four weeks duration (headache, vomiting and vertigo); disseminated signs of cerebral and meningeal involvement; rapid decline and death. Necropsy; multiple metastatic cerebral lesions (primary carcinoma in the left bronchus) with a nodule in the fourth ventricle.*

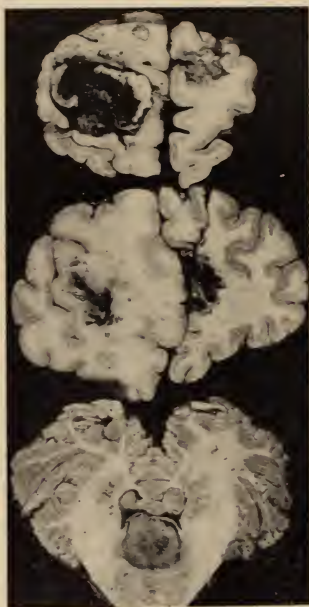


FIG. 1. Coronal sections of the brain showing distribution of the metastatic tumors, particularly the one in the tegmentum of the pons, completely destroying the nuclei of the sixth nerve (Case 1).

*History:* [Adm. 228680; P.M. 4271]. T. B., a woman, aged 52 years, was admitted to the hospital complaining of headache and vomiting of four weeks duration. She had had influenza four years previously. Severe headache, repeated vomiting and pain in the abdomen marked the abrupt onset of the fatal illness. The headaches became constant and grew in severity as the epigastric pain became less constant. The vomiting continued and was not related to meals; it was frequently precipitated by sudden movement of the head. The vomitus contained occult blood.

*Examination.* The patient was somewhat drowsy. The essential neurologic findings included rigidity of the neck, a bilateral Kernig sign, blurring of the nasal halves of the discs,

right hemiparesis with a corresponding increase in the deep reflexes on that side, absence of abdominal reflexes and a positive Babinski sign on the right side.

*Laboratory Data:* A lumbar puncture yielded clear cerebrospinal fluid under moderately increased pressure and contained 100 lymphocytes per cubic millimeter. It was negative otherwise. The blood pressure was 120 systolic and 90 diastolic.

*Course:* During the first few days in the hospital the patient developed slight ptosis of the right eyelid, a sluggish pupillary reaction to light and mild hypalgesia on the right side of the body. Acute epidemic meningoencephalitis was considered as a probable diagnosis, while a cerebral neoplasm was regarded only as a remote possibility. Soon, however, additional symptoms appeared, such as paralysis of upward gaze, weakness of the right internal rectus muscle with poor convergence and tenderness on percussion over the left side of the skull. Meningoencephalitis was still regarded as the most likely diagnosis since the cell count in the cerebrospinal fluid obtained by a second lumbar puncture contained 128 lymphocytes per cubic millimeter. In the course of the third week in the hospital the ptosis of the right upper lid became more pronounced; fixation of the right pupil and paralysis of the internal and superior rectus muscles on the same side, and pronounced papilledema, paralysis of the left abductor muscle in the larynx developed. Gastric analysis revealed absence of free hydrochloric acid and a total acidity of 30 degrees. In view of the values for gastric acidity and the advancing papilledema, a metastatic cerebral neoplasm came under more serious consideration. The condition of the patient declined rapidly and she died on the twenty-fifth day in the hospital.

*Necropsy Findings. General:* Primary carcinoma of the left upper bronchus.

*Brain:* On sectioning of the brain a few small yellowish areas measuring about 1 cm. in diameter were found scattered through the left frontal lobe. They were sharply demarcated from the surrounding brain tissue. The cerebellum exhibited in the white substance of the right lobe a yellowish mass measuring 2 x 3 cm. In the fourth ventricle there was found a spherical tumor measuring about 1.5 cm. in diameter, springing by a narrow pedicle from its floor (fig. 2A).

*Microscopic Observations:* Sections of the several tumor masses disclosed their metastatic carcinomatous character, which was identical with that of the primary growth in the lung. The tumor tissue was made up of numerous alveoli lined by cuboidal epithelium and filled with mucous material. The alveoli were separated from each other by a vascular connective tissue stroma (fig. 2B).

*Comment:* The earlier diagnosis of meningoencephalitis was justified by the precipitate onset, the dissemination of signs, evidence of meningeal irritation and the pleocytosis. On the other hand, the intense headache, the Bruns syndrome (marked vertigo on active movement of the head), the tenderness to percussion and the suggestive gastric analysis were of sufficient significance to arouse more than a suspicion of a metastatic tumor of the brain. But even under such circumstances the primary lesion would most likely be placed in the gastro-intestinal tract, although post-mortem examination revealed that no tumor was present there and that the primary lesion was in the lung.

*Subgroup B.* Here also there are only two cases. In these, however, some symptoms and signs (though not confirmed by x-ray studies) were found during the clinical course.

*Case 3. Emotional instability over a period of years; acute onset of general symptoms of increased intracranial tension with intercurrent development of signs of pulmonary involvement; meager focalizing cerebral signs followed by more discrete focal and general signs of brain tumor; convulsions with death occurring during a convulsion.*

*History:* (Adm. 424805; P.M. 10818). R. M., a married woman, aged 45 years, manifested evidence of emotional instability for many years prior to the onset of her fatal illness. The latter had an acute onset marked by severe headache, nausea and occasional vomiting. On three occasions the headache was unusually severe and was accompanied by momentary loss of consciousness.

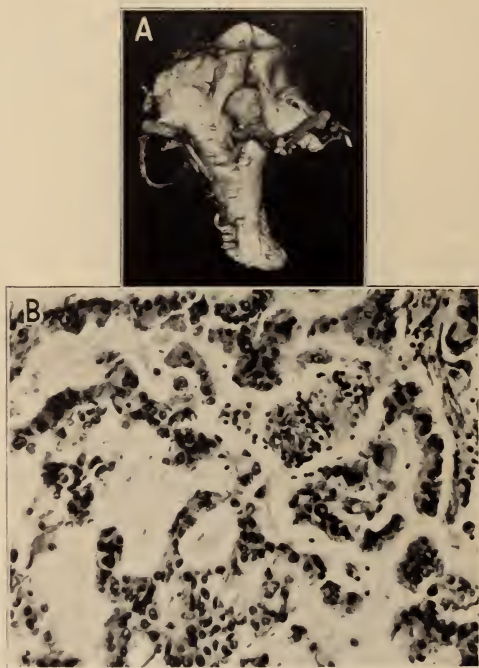


FIG. 2 A. Gross appearance of small metastatic nodule in the floor of the fourth ventricle (Case 2).

B. Histologic character of the metastatic nodule ( $\times 240$ ).

*Examination:* There was dullness over the left upper lobe of the lung with diminished breath sounds. The neurological findings were meager, consisting of diminished swing and some ataxia and adiadochokinesis of the right upper extremity.

*Laboratory Data:* Gastric analysis revealed absence of free hydrochloric acid. Lumbar puncture yielded normal cerebrospinal fluid under normal pressure. The total protein was 67 mg. per cent.

*Course.* The patient's complaints were regarded primarily due to emotional instability and plans were made for her transfer to the Mental Health Clinic. But while still in the

hospital she suddenly passed through an episode of unconsciousness which was accompanied by right sided pyramidal tract signs and followed by a mild transient aphasia. Blood sugar taken at that time was 80 mg. per cent. A subsequent neurological examination revealed, in addition to the earlier finding of ataxia of the right arm, right ankle clonus and a poor right plantar response. The disc margins were found to be somewhat hazy. The diagnosis of an expanding lesion of the left hemisphere was then made, but the patient would not submit to operation and left the hospital.

At home her headaches became constant and more severe; she vomited two to three times daily and developed a *cough productive of small amounts of foul smelling material.*



FIG. 3. Cross section of the pons and parts of the cerebellum showing the large tumor nodule (Case 3).

*Second Admission:* She re-entered the hospital four days later. The disc margins were blurred, the left pupil was larger than the right; there was a slight right central facial weakness with mild pyramidal tract signs on the right side and markedly depressed abdominal reflexes on the same side. Another lumbar puncture yielded cerebrospinal fluid under an initial pressure of 180 mm. of water. Two days later the patient had another convulsive seizure lasting one minute. It was preceded by pain in the head and followed by deviation of the eyes upward and to the left and convulsive movements of the left arm. Bronchoscopy was attempted, but the first spray of cocaine resulted in the complaint of faintness followed immediately by loss of consciousness and clonic movements of the left arm and later of the right leg. The eyes deviated upward and to the left. The patient regained consciousness five minutes later. Bronchoscopy was not again attempted. She died the following day during another convulsive seizure.

*Necropsy Findings. General:* Carcinoma of the left lung with metastases to pleura, pericardium, liver, kidneys, adrenals, lymph nodes and brain; pericardial effusion; coronary arteriosclerosis without narrowing; thickening of the mitral valve; congestion of the spleen, liver and kidneys; primary infect, right lower lobe; old pleural adhesions.

*Brain:* In the right temporo-occipital region there was found a cavity which measured about 2 cm. in diameter filled with a yellowish white material. In the precentral gyrus, in the arm area, there was a small circular yellowish area measuring about  $\frac{1}{2}$  cm. in diameter. In the right cerebellar hemisphere which appeared larger than the left there was a large hard nodule almost completely displacing the dentate nucleus (fig. 3). Areas of yellowish discoloration were found on the mesial aspect of the left hemisphere in the frontal area, in the right posterior portion of the inferior temporal convolution, and in the anterior one-third of the right third of the right occipital lobe. All these areas were zones of metastatic tumor formation. Another small nodule was found in the superior temporal convolution of the left hemisphere.

*Microscopic Observations:* Several sections of tumor tissue stained with hematoxylin and eosin showed well circumscribed areas of metastatic tumor tissue adjacent to and infiltrating disorganized cortical tissue. Epithelial cells were arranged in acinar and papillary formations. The tumor cells were cylindrical in type and formed papillary projections. There were many goblet cells. In some areas the columnar cells were pseudo-stratified. The cell cytoplasm stained uniformly pink and their nuclei were large, ovoid, basophilic, and vesicular in appearance. Many mitotic figures were seen. Many multinucleated giant cells, as well as other neoplastic cells were seen between the larger metastatic acini. There were many areas of necrosis bordering upon the area invaded by the tumor tissue. Section from the tumor in the right cerebellar hemisphere revealed lakes of pale pink homogeneously staining material in between the acini and papillary projections. In some areas these lakes were densely infiltrated with leucocytes and lymphocytes. Compound granular cells and multinuclear giant cells were also present.

*Comment:* The severe headache and other signs of increased intracranial tension in contrast to the few focalizing signs of brain involvement during the early part of the clinical course is not an uncommon occurrence in metastatic brain tumor.

*Case 4. Sudden onset of recurrent severe headache; gradual development of left hemiparesis; clubbed fingers; repeated convulsive seizures; terminal bronchopneumonia.*

*History:* (Adm. 478162; P.M. 11986). S. F., a man, aged 63 years, eight weeks before admission to the hospital began to complain of constant headache, often so severe that sleep inducing medication had to be administered. The pain was accentuated by movement of the head and also by combing his hair. One week after the onset of his symptoms he had a shaking chill with elevation of temperature to 103°F. The day after the chill he felt too weak to get out of bed and noticed weakness and swelling of the left hand and wrist. A brief period of improvement followed, but two weeks later weakness of the lower limbs, unsteadiness of gait and a general feeling of heaviness set in. Two days before admission to the hospital the patient had a convulsive seizure.

*Examination:* Left central facial weakness, weakness and swelling of the left hand, increased deep reflexes on the left side with diminution of abdominal reflexes on the same side, suggestive Hoffman, Chaddock and Oppenheim signs on the left and a left sided ataxia with a rebound phenomenon on that side, slight past-pointing on the left with the left upper extremity, diminished sensation to pin-prick in the left hand and forearm, slight impairment of position and two point discrimination in the left hand, a right middle ear deafness, ataxic and broad-based gait, and a Romberg sign with swaying to the left were the significant neurological findings. *There was marked clubbing of the fingers.*

*Laboratory Data:* Lumbar puncture yielded cerebrospinal fluid under an initial pressure of 130 mm. of water with a Pandy reaction of 2 plus and total protein of 112 mg. per cent. X-ray examination of the chest showed a faint circumscribed infiltration about 2 cm. in diameter at the level of the third rib on the right. It resembled an old tuberculous lesion. There was no evidence of metastasis.

*Course:* Multiple lesions, probably metastatic, were postulated because of the presence of both cerebral and cerebellar signs. On the third day in the hospital the patient had a generalized convulsion involving the left extremities more than the right and lasting about 5 minutes. It was preceded by an increase in severity of the headache and the development of nausea, and was followed by a period of stupor lasting about ten minutes, during which period the pupils were dilated and failed to react. There was a positive Babinski sign on the left and the patient was incontinent. One hour later there was a similar attack, involving especially the left lower face, the left arm and leg. The episode lasted about 5 minutes following which the patient's left sided weakness was increased. Thereafter the positive Babinski, Gordon and Oppenheim signs on the left persisted, but the headache diminished in intensity. One week after admission his speech became thick and slow. A ventricu-

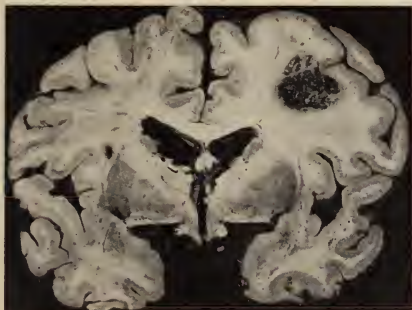


FIG. 4. Coronal section of the brain showing appearance and location of the metastatic tumor (Case 4).

lography disclosed an "internal hydrocephalus." Following this procedure the patient passed into stupor and developed twitchings of the right extremities. Because of the increasing stupor, ventricular tap was repeated. An increased pressure was found and relieved, but both the stupor and twitchings continued. The patient developed a bronchopneumonia and died during the fifth week in the hospital.

*Necropsy Findings. General:* Small carcinoma of the upper lobe of the right lung; chronic pneumonia; encapsulated empyema between the left lower lobe and diaphragm; emphysema and edema of the lungs; hypertrophy and dilatation of the right ventricle; pleural adhesions of both lungs; moderate arteriosclerosis of kidneys; adrenal rest right kidney; acute infectious splenitis.

*Brain:* A patch of yellowish discoloration was noted on the orbital surface of the left frontal pole, apparently localized to the leptomeninges. The right precentral gyrus was found to be somewhat elevated and softer on palpation than the adjacent tissue. On sectioning the brain an irregularly circular yellowish-grey tumor mass, measuring  $2\frac{1}{2}$  cm. was found in the right fronto-parietal region straddling the central fissure and extending into the pre- and post-central gyri, on a level with the mid-frontal convolution (fig. 4). It was surrounded by a wide zone of edema.

*Microscopic Observations:* Sections taken through the tumor and stained with hematoxy-

lin and eosin showed a large central area of softening occupied by fibrinous and hyaline material. Lining this area, and lying in disorganized cerebral substance, were many nests of large cuboidal cells arranged in alveolar pattern around small capillaries. These cells had round, centrally placed nuclei, the chromatin content of which varied greatly. Many cells showed mitotic figures. A few bizarre giant cell forms were found containing one very large or multiple nuclei. Many swollen glial and compound granular cells were found there.

*Comment:* Signs of pulmonary involvement were meager, but nevertheless significant consisting as they did only of the clubbing of the fingers. Significant also is the frequency with which convulsive seizures are encountered in metastatic cerebral lesions.

*Subgroup C.* This subgroup contains seven cases.

*Case 5. Acute onset of obstinate constipation, followed by recurrent attacks of severe headache; intercurrent mildly productive cough; terminal cerebral manifestations.*

*History:* (Adm. 448562; P.M. 11333). A man, aged 60 years, three months before admission to the hospital developed obstinate constipation, and attacks of vomiting after meals. There was a rapid loss of weight. During the second month of his illness he began to experience severe headache. Mental changes characterized by confusion and drowsiness followed. He took to bed during the last ten weeks of his illness and at this time developed a slight cough with some expectoration.

*Examination:* The patient was confused and lethargic. There was moderate bilateral papilledema. There was a definite right supranuclear facial weakness, and marked weakness of the right upper extremity. The deep reflexes were all depressed and the ankle jerks were not elicited. Inconstant Oppenheim and Babinski signs were elicited on the right side. The abdominal and cremasteric reflexes were absent on the right side.

*Laboratory Data:* Hemoglobin, 111 per cent; 24,000 white blood cells with 81 per cent polymorphonuclear leucocytes and 11 per cent lymphocytes.

*Course:* The patient became progressively more lethargic to the point of semi-stupor, developed Cheyne-Stokes respirations, urinary and fecal incontinence, and died five days after admission to the hospital.

*Necropsy Findings. General:* Bronchogenic carcinoma with diffuse submucosal and lymphatic infiltration, right lower lobe; metastases to mediastinal and mesenteric lymph nodes; multiple metastases to skull, vertebrae, both adrenals, wall of stomach and small intestines and right kidney.

*Brain:* Sectioning of the brain showed a large number of metastatic nodules varying in size from 2 mm. to 1½ cm. They were found throughout the cortex and subcortex of the cerebrum and cerebellum (fig. 5). A fairly large tumor was also found in the floor of the fourth ventricle. About twenty of these nodules were counted, but this number did not exhaust all the metastatic nodules that could be found by further cutting.

*Microscopic Observations:* Sections of the metastatic nodules stained with hematoxylin and eosin showed tissue within the nodule to consist of many pleomorphic cells with pleomorphic nuclei. Occasionally there was a tendency for these cells to aggregate themselves around the blood vessels of the tumor (fig. 6).

*Comment:* The obstinate constipation could have been considered as pointing to the gastro-intestinal tract as the site of the primary lesion. Post-mortem study, though disclosing involvement of the latter, nevertheless showed it to be secondary in character.

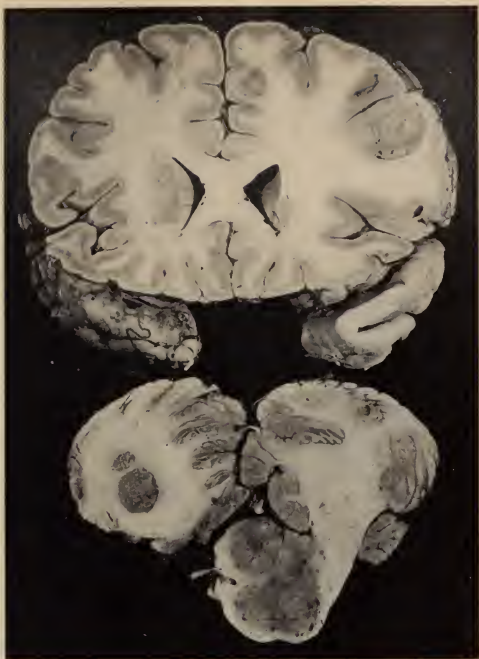


FIG. 5. Coronal section of the brain and brain stem showing a few metastatic nodules. One is seen in the left frontal lobe and two are noted in the white matter of the cerebellum, while four are seen in the cortex of the cerebellum. A large one is seen in the tegmentum of the pons (Case 5).

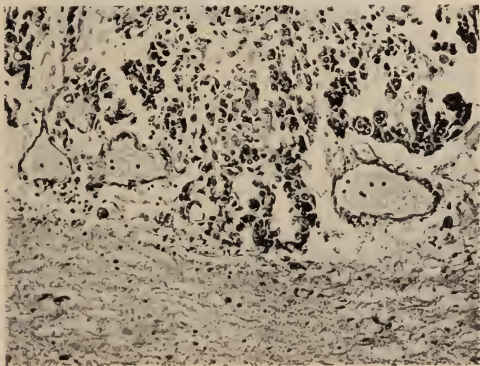


FIG. 6. Histologic appearance of the metastatic nodules (Case 5) ( $\times 200$ )

*Case 6.* A long history of recurrent psychoses; sudden onset of headache, nausea and vomiting, followed by general weakness and manifestations of cerebellar involvement; rapid decline with development of pulmonary signs and symptoms.

*History:* (Adm. 447872; P.M. 11335). A man, aged 55 years, had been confined to mental hospitals on four occasions for periods of five years each time, finally being discharged from a mental institution in 1935. Six weeks before admission to this hospital he began to complain of headache. Two weeks later he became subject to daily attacks of nausea and vomiting. He staggered, complained of dizziness and generalized weakness. A few days before entering the hospital he became drowsy and uncooperative.

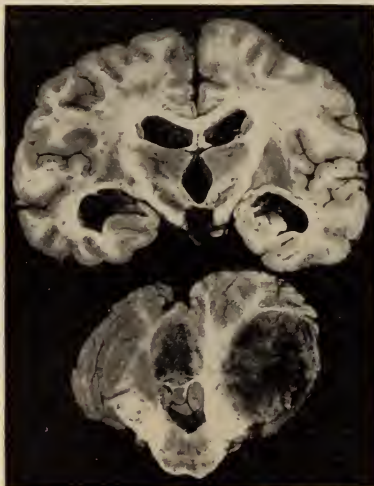


FIG. 7. Coronal section of the brain showing symmetrical internal hydrocephalus and the two metastatic tumors in the cerebellum (Case 6).

*Examination:* The patient was somnolent, disoriented for time and place. In his speech he exhibited anomia and perseveration. He tended to hold his head with the occiput tilted to the right shoulder. The right arm drifted downward on extension. There were adiochokinesis and dysmetria of the right upper extremity without ataxia. The right abdominal reflexes were less active than the left. There was an inconstant bilateral Babinski sign.

*Laboratory Data:* Ventriculography showed symmetrical dilatation of the lateral and third ventricles. X-ray examination of the chest showed a widened upper mediastinum, but no significant abnormalities were noted.

*Course:* A few days after admission the patient coughed up blood-streaked sputum. He became confused, drowsy, developed neck rigidity and bilateral Kernig sign. There were occasional nystagmoid jerks. The deep reflexes disappeared, but a definite Babinski sign appeared on the left. A lumbar puncture yielded clear cerebrospinal fluid under an initial

pressure of 130 mm. of water; there were no cells. The patient died 23 days after admission to the hospital.

*Necropsy Findings. General:* Carcinoma of the right main bronchus with metastases to regional lymph nodes and extension to left main bronchus, superior vena cava, and esophagus; focal bronchopneumonia; congestion and edema of the lungs; moderate dilatation of the left ventricle of the heart; congestion of spleen and kidneys; small benign polyp of sigmoid colon.

*Brain:* The right cerebral hemisphere appeared larger and firmer than the left. The right lobe of the cerebellum also was larger than the left. Two large tumor masses were present in the cerebellum (fig. 7). The largest, measuring 4 cm., was situated in the ventral two-thirds of the right cerebellar hemisphere. The other mass, measuring 2½ cm. was situated in the vermis and almost completely replaced it. The tumor masses were clearly demarcated from the adjacent tissue by color and structure.

*Microscopic Observations:* Sections of the tumors of the cerebellum revealed very cellular tissue broken up into irregular mosaic forms by cores of connective tissue. The nuclei were large, surrounded by very little cytoplasm. The connective tissue was in places very abundant, and within the structure there were many vessels with hypertrophied walls and filled with blood. An area of necrosis was present in one part of the tumor. The cerebellar tissue adjacent to the tumors showed infiltration of neoplastic cells, disorganization and congestion of blood vessels.

*Comment:* The dominant signs of cerebellar involvement are in full accord with the presence of massive cerebellar lesions.

*Case 7. Sudden onset of hemiparesis, accompanied by headache and followed by mental deterioration; focal signs and encephalography pointed to expanding lesion; pulmonary signs not conclusive; craniotomy; death.*

*History:* (Adm. 368533; P.M. 9277). A man, aged 64 years, stumbled and fell two weeks before admission to the hospital. During the next two days he developed a mild confusion and memory defect. Further questioning yielded the fact that the patient had a cough for five months and hemoptysis for two months before the onset of his present illness.

*Examination:* The neurologic findings included a left homonymous hemianopsia, weakness on the left side with generalized hyporeflexia; a left Babinski sign on the left and equivocal plantar reflex on the right, and slight left hemihypesthesia for all modalities. There were diminished breath sounds posteriorly. The heart was enlarged to the left; a soft diastolic murmur was heard at the base.

*Laboratory Data:* The cerebrospinal fluid was clear; globulin, 4 plus; total protein, 90 mg. per cent, negative in all other phases. X-ray examination of the chest showed nothing definite. Encephalography showed a shift of both ventricles to the left, with incomplete filling of the right.

*Course:* An exploratory craniotomy was performed and a tumor removed from the parieto-occipital area. The patient died one day following the operation.

*Necropsy Findings. General:* Primary carcinoma of the right main bronchus with metastases to the tracheo-bronchial and perigastric lymph nodes, lungs and left suprarenal gland; fibrous pleuritis; thrombosis of the left femoral vein and its tributaries; edema of the left lower extremity; multiple emboli of pulmonary arteries; fatty changes of liver; partially obliterated appendix.

*Brain:* There was an excavated area involving the entire width of the occipital lobe and about 2 cm. in the vertical plane and involving the posterior third of the parietal lobe and the anterior half of the occipital area. This defect showed a very irregular interior, discolored, showing little which could be identified as brain tumor. A small piece of tissue was found in its depth which was neoplastic.

*Microscopic Observations:* Sections of the tumor tissue stained with hematoxylin and eosin showed it to be bordered on its free surface by a fibrous capsule of varying thickness which was quite likely the pia-arachnoid. Fibrous septa divided the tumor cells into islands or lobules of varying size and shape. The densely packed tumor cells were large, polygonal, had a coarsely granular cytoplasm, and a large nucleus which stained deeply and homogeneously. There were many mitotic figures. The central portion of the tumor had undergone degeneration. There was marked increase in glial nuclei and rarefaction of the tissue.

*Comment:* Metastatic tumors, though single, when primary in the lung, offer little promise for surgical intervention.

*Case 8. Cerebral symptoms of six months duration, preceded by pulmonary manifestations of five years duration. Disseminated neurologic signs, including those of meningeal involvement; terminal psychosis; rapid decline; death, without operation; necropsy, metastatic carcinomatosis of the brain and meninges.*

*History:* (Adm. 247660; P.M. 4825). F. M., aged 44 years, was subject to an occasional attack of dyspnea on slight exertion, weakness and palpitation, associated with a mild but persistent cough, without hemoptysis or night sweats, over a period of five years preceding the onset of the fatal illness. The latter began six months prior to his admission to the hospital when he became aware of a noise in the head and ears and developed general malaise, accompanied by loss of weight. Four months later his voice suddenly became hoarse and in another five weeks his vision became impaired and he began to experience severe, knife-like pain between his shoulder blades. Shortly thereafter severe occipital headache set in, accompanied by attacks of dizziness.

*Examination:* There were moist râles throughout the chest. The pupils were irregular and unequal, the left being fixed to light, while the right eyelid was ptosed. Weakness of the left side of the face and slight paresis of the left arm were present. Some impairment of motion of the left side of the palate and a cadaveric position of the right vocal cord were noted on laryngoscopic examination. There were mixed deafness on the right side and total deafness on the left. The deep reflexes in the upper extremities were active and equal; the knee jerks were absent, and the abdominal reflexes were diminished. Roentgenographic examination of the chest revealed nothing abnormal.

*Course:* Meningoencephalitis, either syphilitic or tuberculous, was among the diagnostic possibilities, but a diffuse neoplastic process was also considered. Rapid decline, marked by intensification of the meningeal signs, increased rigidity of the neck, a more pronounced bilateral Kernig sign, complete areflexia and psychotic manifestations led to the patient's death on the tenth day in the hospital.

*Necropsy Findings. General:* There was a primary adenocarcinoma in the right upper bronchus, with metastases to the regional lymph nodes, the pericardium and the recurrent laryngeal nerve.

*Brain:* The left optic nerve showed a bulbous swelling extending from a point a little above the optic tract, which appeared to be invaded by a tumor; this mass was deep gray, firmer than the right nerve and measured from 5 to 6 mm. in diameter. A short distance to the left of this mass was another, a grayish white, firm tumor about 2 mm. in diameter. No other tumor could be seen anywhere over the surface of the brain or along any of the other cranial nerves.

*Spinal Cord:* There was a bulbous enlargement in the region of the ninth to the twelfth dorsal segment. Externally this portion of the cord was of normal color, but of slightly increased firmness. The meninges covering the spinal cord showed no gross pathologic alterations. The spinal nerves likewise were all grossly normal.

*Microscopic Observations:* Sections of the cerebral cortex with its meningeal coverings, the brain stem, the left optic nerve (fig. 8), and the spinal cord showed diffuse metastatic infiltration of the meninges and, in isolated areas, of the nerve tissue. The histologic

appearance was that of an adenocarcinoma and was similar to that of the primary mass in the bronchus. The neoplastic cells formed acini and other groups, separated by a connective tissue stroma. The cells and their nuclei varied in size and shape, the cells tending to be columnar. Often two or more layers of cells lined the acini, and occasionally the cell outlines were so indistinct as to give the appearance of a syncytium.

*Comment:* The tinnitus and the partial aphonia, the radicular pain in the upper dorsal region, the loss of deep reflexes in the lower extremities accompanied by symptoms of increased intracranial tension, such as headache and dizziness, pointed strongly to a meningeal process, disseminated in character, involving the

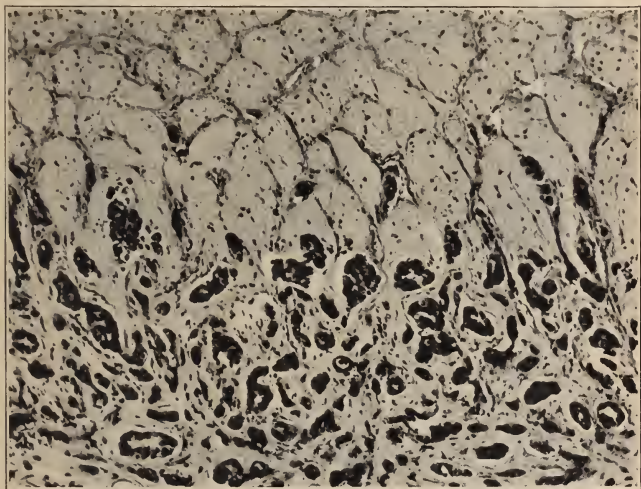


FIG. 8. Cross section of the optic nerve showing its infiltration with carcinomatous (metastatic) cells along the meningeal extensions (Case 8) ( $\times 105$ ).

brain, the spinal cord and the spinal roots. The paresis of the right arm indicated that the process extended into the brain substance, justifying the diagnosis of a diffuse meningoencephalitic process. The repeated failure to find the tubercle bacilli and negative Wassermann reactions of the blood and the cerebrospinal fluid excluded both tuberculosis and syphilis as the causative factors. Thus, a neoplastic process involving diffusely the meninges and the adjacent brain structure was the most likely condition.

*Case 9.* Productive cough of two years duration; cerebral manifestations of three months duration; neurologic signs pointing to probable thrombosis of the left middle cerebral artery, of syphilitic or arteriosclerotic origin; rapid decline; terminal bronchopneumonia; necropsy.

*History:* (Adm. 438497; P.M. 11201). A man, aged 65, three months before admission to the hospital began to experience difficulty in writing, attributed to weakness of the right hand. During the subsequent two months the weakness spread to the right leg. Somewhat

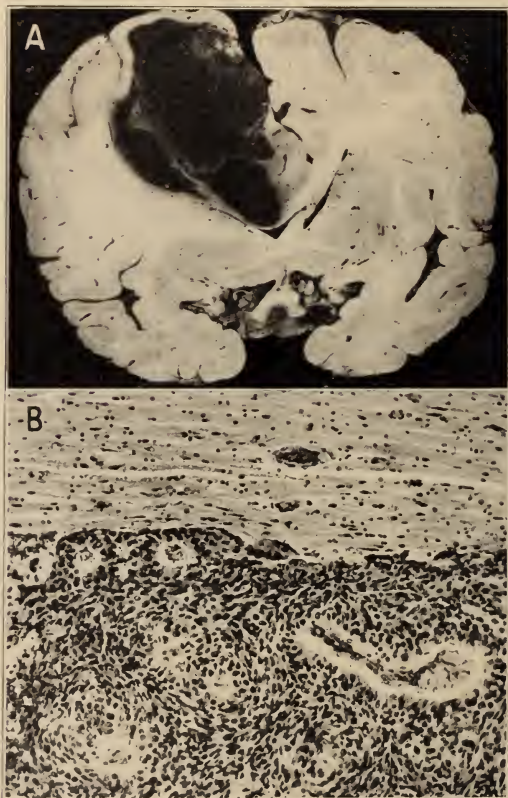


FIG. 9A. Gross appearance of the tumor showing its rich vascular supply and sharp demarcation (Case 9).

B. Histologic character of the tumor. Here, again, the sharp deliniation is well demonstrated ( $\times 90$ ).

later his speech became impaired, so that he was unable to find the desired words for expression. He had had a productive *cough and dyspnea* on exertion for two years and a 4 plus blood Wassermann reaction in 1937 at which time he was given anti-syphilitic treatment.

*Examination:* The patient was moderately euphoric, speech was intact. The pupils were slightly irregular but reacted well to light and in accommodation. The upper and lower extremities on the right side were weak and were held in the attitude of spastic hemiplegia. On the right side the deep reflexes were hyperactive, the abdominal reflexes were absent and a Babinski sign was elicited. Vibratory sense was absent below the anterior iliac crest on both sides. *The heart and lungs were normal.* The blood pressure was 130 systolic and 70 diastolic.

*Laboratory Data:* A lumbar puncture yielded normal cerebrospinal fluid under normal pressure. The Wassermann reaction of the blood was 4 plus.

*Course:* The diagnosis of thrombosis of the left middle cerebral artery, with either syphilis or arteriosclerosis as the causative factor was considered as most likely. Anti-syphilitic therapy was administered for four weeks with but slight improvement. At the end of this period (May 9) the patient suddenly became disoriented and confused, the aphasia became more pronounced and the hemiplegia became complete. He became incontinent of urine and feces. His condition declined steadily during the next six weeks, terminal bronchopneumonia developed and he died.

*Necropsy Findings. General:* Primary carcinoma of the upper lobe of the left lung.

*Brain:* A large area of discoloration was found in the left cerebral hemisphere (fig. 9A), extending from a point at the level of the genu of the corpus callosum as far back as the splenium. It was delimited from the adjacent tissue by a well defined margin of pearly white tumor tissue. The mass was somewhat lobulated, presenting two main parts. At the periphery it showed a small island of hemorrhagic material, again well delimited from the adjacent tissue.

*Microscopic Observations:* The tumor mass (fig. 9B) consisted of numerous islands of neoplastic cells, irregularly separated from one another by wide zones of extravasated blood. Throughout the tumor there were trabeculae of connective tissue, containing many blood vessels. The cerebral substance adjacent to the tumor showed rarefaction of tissue, vascular congestion, increase in glial nuclei and moderate degenerative alterations in the nerve cells.

*Comment:* The rather abrupt onset of symptoms and signs pointing to a discrete lesion in the left hemisphere in a patient of advanced years who was known to have had a positive Wassermann reaction of the blood, justified the original diagnosis of a vascular process in the brain, either syphilitic or arteriosclerotic in origin. But the pulmonary symptoms such as productive cough and dyspnea on exertion should have aroused the suspicion of a probable malignant process in the lungs. Roentgenographic examination of the chest probably would have established the diagnosis.

*Case 10. Acute signs and symptoms pointing to bulbar involvement; diagnosis of infiltrating tumor of the pons; roentgen therapy; progressive decline; death.*

*History:* (Adm. 470360; P.M. 11801). D. S., a man, aged 56 years, was apparently well until two months before his first admission to the hospital. He first noticed impairment of handwriting; one week later he began to experience double vision on looking to the left, and his speech became slurred. The succeeding weeks were marked by progressive increase in weakness of his arms and legs. While the left extremities seemed to improve in strength the weakness of the right extremities remained unchanged. Three weeks before admission to the hospital intermittent headaches, increasing in severity, set in. They were accompanied by a disturbing drilling noise in the left side of the head. Shortly thereafter the patient found that he could not completely close his left eye and that the muscles of the left side of the face were weak; hearing in his left ear became impaired.

*Examination:* (First Admission). Horizontal nystagmus on left lateral gaze and rota-

tory nystagmus on upward gaze; palsy of the left external rectus muscle; hypesthesia of the left cornea; weakness of the left side of the face of the peripheral type; diminution of hearing on the same side with deviation of the tongue to the left; deviation of the soft palate to the right; slurring of speech; weakness and hyperactive deep reflexes with an equivocal Babinski sign on the left side, and reduced perception of pain on the entire right side, including the head, were the more significant neurologic findings. There was bilateral ataxia on finger-to-nose and heel-to-knee tests, more noticeable on the right side. The gait was broad based and unsteady.

*Laboratory Data:* Roentgen examination of the skull and of the chest were reported to show nothing significant. Complete examination of the blood and urine gave normal results.

*Course:* A neoplasm in the brain stem was considered, not to the full exclusion of a vascular lesion. Roentgen therapy was begun and then was discontinued because of an untoward reaction. The patient was allowed to return home. There was temporary improvement in power, while vision and hearing grew worse and the weakness of the right arm and



FIG. 10. Section of the brain stem with the overlying cerebellum showing the character and location of the tumor.

leg increased. He began to experience difficulty in swallowing and returned to the hospital.

*Examination (Second Admission).* Nystagmus on right lateral gaze, paralysis of the left external rectus muscle, right hemiparesis, with a Hoffman sign and ankle clonus on the same side, partial paralysis of the left facial nerve of the peripheral type, thick and slurred speech set in, and swallowing was difficult.

*Course:* A lumbar puncture yielded cerebrospinal fluid under an initial pressure of 300 mm. of water. The Pandy reaction was 4 plus, and there were 11 large mononuclear cells per cubic millimeter. An infiltrating neoplasm in the brain stem was now diagnosed. During the following three and a half months his condition declined progressively and terminated in death.

*Necropsy Findings. General:* Primary carcinoma arising from the bronchus of the upper lobe of the right lung.

*Brain:* The pons was the seat of a large tumor which occupied practically all the tegmentum and part of the basis pontis, leaving a narrow zone dorsally and a still narrower one ventrally (fig. 10). When traced anteriorly the mass was observed to terminate at the level of the nucleus of the trigeminal nerve.

*Microscopic Observations:* The tumor mass consisted of columns of neoplastic cells, each zone being separated by a connective tissue stroma, thru which ramified numerous blood vessels. There was a tendency for the neoplastic cells to form acini, and in such instances the cells were typically columnar, with a small, moderately chromatinized nucleus situated at the base of the cell. The center of the acini contained some desquamated epithelial cells, with a few lymphocytes and polymorphonuclear leucocytes. Usually the neoplastic cells formed broad sheets with no semblance of acini formation. In such instances the cells were necrotic and assumed bizarre shapes and sizes. Intermingled with these were also necrotic blood elements and macrophages.

*Comment:* The clinical manifestations were in accord with a pontile lesion. The negative roentgenograms of the chest made it difficult to recognize the metastatic character of the lesion.

*Case 11. History of loss of weight for seven months and pain in right lower posterior portion of the chest; appendectomy; lump in the submaxillary region; no neurologic signs; roentgenographic evidence of a malignant progress in the ribs and spine; biopsy showed the cervical gland to be the seat of a metastatic adenocarcinoma; pathologic fracture of rib; terminal bronchopneumonia.*

*History:* (Adm. 403521; P.M. 10237). A man, aged 35 years, was apparently well until seven months before admission to the hospital when he suddenly experienced a sharp pain in the right lower posterior portion of the chest and the right loin. The pain recurred several times, and two months later an appendectomy was performed for its relief. After the operation he began to have pains in the left side of the chest, and a productive cough developed. The pains in the right groin spread to the right thigh. Pain in the back of the neck, flushing and excessive perspiration, especially at night, followed. One week before admission he noted a non-tender lump in the right submaxillary region.

*Examination:* There were no neurologic findings. The blood pressure was 110 systolic and 72 diastolic. The prostate was hard and nodular. There was a subcutaneous nodule at the upper end of the right sternocleidomastoid muscle. The lungs were normal.

*Laboratory Data:* Roentgenograms of the lungs and skull were reported as negative; roentgenographic examination of the spine showed some areas of rarefaction in the sixth dorsal vertebra and the fourth, tenth and eleventh ribs, raising the suspicion of a malignant growth.

*Course:* A diagnosis of carcinoma of the prostate gland with multiple metastases to the spine was considered. The subcutaneous nodule in the neck was excised and was reported as containing adenocarcinoma of the mucous cell type. It was then thought that the primary site was in the respiratory tract. A pathologic fracture of the sixth right rib occurred, accompanied by a cough with bloody sputum. *Dullness on percussion developed in the upper lobe of the left lung.* Death occurred at the end of four weeks in the hospital.

*Necropsy Findings. General:* Primary carcinoma of the mucous cell type of the lower lobe of the left lung, with extensive metastases to the abdominal and thoracic organs.

*Brain:* A small well circumscribed, slightly hemorrhagic area, measuring  $\frac{1}{4}$  inch in diameter, was found in the right temporal lobe. In the left temporal lobe there was a small area of softening in the cortex of the second temporal gyrus. A third lesion was noted on the ventral aspect of the left temporal lobe. This measured  $\frac{1}{4}$  inch in diameter and was well circumscribed with a greenish, gelatinous appearance.

*Microscopic Observations:* Sections of one of the tumor masses showed the cells to be arranged in an acinous or papillomatous formation. The stroma of connective tissue serving as the core of the villus-like projections was thin and contained thin-walled blood vessels. For the most part, one layer of neoplastic cells formed the lining of the acini. The cells were columnar, and their small round or oval nuclei were situated at the base of the cells. The acini contained mucus-like material and often desquamated tumor cells.

*Comment:* The relatively small size of the lesions, their distribution in relatively silent areas of the brain and their probable recent development explain the absence of focalizing neurological signs.

*Subgroup D.* The last subgroup in which the primary source of the lesion was disclosed by clinical studies and confirmed by x-ray examination of the chest is also quite a large one, consisting of seven cases.

*Case 12. Sudden onset of signs and symptoms pointing to pulmonary malignancy; no neurologic signs or symptoms; metastatic lesions in the brain discovered at autopsy.*

*History:* (Adm. 468219; P.M. 11796). C. C., a man, aged 47 years, took ill suddenly three months before admission to the hospital, complaining of anorexia, easy fatigability. He became subject to a cough productive of white mucoid material. With this he experienced pain in the left chest. Two chest taps were performed, one yielding thick material, the other thin sanguinous material.

*Examination:* The only positive neurologic finding was a slight irregularity of pupils which were small and reacted sluggishly to light and in accommodation. The patient was dyspneic and cyanotic. The trachea was deviated to the left. At the base of the left lung there were flatness and absent breath and voice sounds. Diminished bronchial breathing and whispered pectoriloque was present above this area. A vaguely definable tender mass, moving with respiration, was palpable in the right quadrant of the abdomen.

*Laboratory Data:* Blood: hemoglobin, 67 per cent; white blood cells, 14,000 with 89 per cent polymorphonuclear leucocytes; 8 per cent lymphocytes; and 4 per cent monocytes. Blood Wassermann reaction, 4 plus. Urine: faint trace of albumin, occasional white blood cell. An electrocardiogram revealed left axis deviation. Aspiration of the left chest revealed bloody fluid, cultures of which yielded pneumococcus type 3. X-ray examination of the chest revealed an homogeneous density obscuring the entire left hemithorax. Intravenous pyelogram was essentially negative.

*Course:* The patient was given sulfapyradine and his temperature, which had been elevated, returned to normal. Bronchoscopy revealed a carcinoma of the bronchus, and biopsied material revealed an anaplastic carcinoma. With the discontinuation of sulfapyradine the temperature rose again. He developed severe pain in the neck, accentuated by rotation and anterior flexion of the neck. His condition declined progressively and he died on the forty-eighth hospital day.

*Necropsy Findings. General:* Carcinoma of the left lower lobe bronchus with infiltration of the lung; obstruction of both left bronchi; atelectasis of bronchiectasis; necrosis of the lung and abscess formation; multiple metastases to the periphery of the left lung, right lung, liver, gall bladder, spleen, pancreas, left kidney, peritonum and brain. Confluent bronchopneumonia and fibrinous pleuritis, right lung; pulmonary emphysema and edema; pericardial effusion; double ostium of right coronary artery; arteriosclerosis of the aorta; acute splenitis; small cortical scars of the kidneys.

*Brain:* On sectioning of the brain several tumor nodules were found in the cerebral hemispheres and one large nodule in the cerebellum. Of those in the cerebral hemispheres two were found on the right and a large number of smaller nodules varying in size from pin-point to about 2 mm. were found scattered throughout both hemispheres (fig. 11). The largest tumor mass was in the left cerebellar hemisphere directly outside the middle cerebellar peduncle and limited entirely to the cerebellar cortex.

*Microscopic Observations:* A section of the cerebellum stained with hematoxylin and eosin showed a large area of hemorrhagic necrotic tissue around which and within which there were collections of large tumor cells showing moderate variation in size and shape. These cells had a large amount of cytoplasm and large nuclei, containing a moderate amount of

chromatin material; some of the nuclei had fairly large dense nucleoli. Numerous mitotic figures were seen. Three sections of cerebral cortex stained with hematoxylin and eosin contained nodules of the tumor cells surrounded by areas of hemorrhage and necrosis.

*Comment:* The absence of manifestations of focal cerebral disease and the presence of evidence of cerebrospinal syphilis could hardly have led one to suspect the existence of metastatic lesions in the brain. Their small size, distribution and probable terminal appearance may serve as an explanation for the lack of clinical signs pointing to their existence.

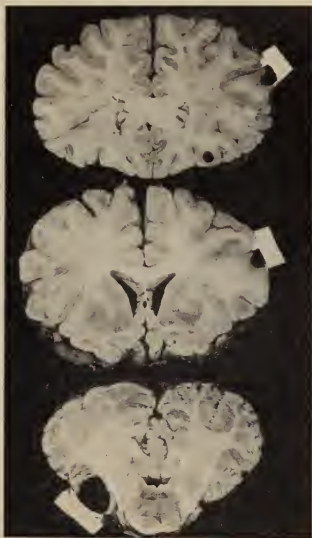


FIG. 11. Coronal sections of the brain showing the appearance of several of the metastatic lesions in the brain (Case 12).

*Case 13. Pulmonary symptoms of one years duration followed by difficulty in swallowing; generalized weakness; no neurological signs; rapid terminal decline.*

*History:* (Adm. 394245; P.M. 9958). M. M., a woman, aged 41 years, noted one year before admission to the hospital tickling sensations in her throat, accompanied by a mild non-productive cough. Shortly thereafter she began to have difficulty in swallowing, at first of solids and then fluids. The cough became progressively worse. She developed generalized weakness and lost weight rapidly. At the end of six months she noted a mass on both sides of her neck. This was particularly noticeable when food was being swallowed. Shortly before entering the hospital she brought up some foul smelling mucoid material.

*Examination:* Neurological status was entirely negative. She showed a state of marked

undernourishment and would frequently be seized by a hollow brassy non-productive cough. There were no other positive findings.

*Laboratory Data:* X-ray examination of the chest suggested a parenchymal neoplasm of the right lower lobe and esophageal diverticulum. Bronchoscopic findings were considered to be "the result of a mediastinal carcinoma."

*Course:* Two weeks after admission to the hospital thoracentesis was done. Following this procedure the patient failed rapidly and died on the eighteenth day in the hospital.

*Necropsy Findings. General:* Carcinoma of the right lower lobe with surrounding pneumonic areas and metastases to right adrenal, mediastinal lymph node with compression of esophagus; deep cervical lymph nodes with compression of the right recurrent laryngeal nerve; caseous tuberculosis of the right upper lobe with cavitation; primary complex peribronchial lymph node, left upper main bronchus; pulmonary effusion; chronic adhesive pleuritis; cholelithiasis; cortical cysts of left kidney; congestion of liver and spleen; chronic interstitial valvulitis.

*Brain:* A small nodule of friable material projected from the lateral surface of the left temporal lobe for a distance of about 1 cm. On coronal section the nodule was seen to be very sharply demarcated from the adjacent cortex and the white matter. In the region of the fornix at about its border the vessels appeared blackened and thrombosed in cross section.

*Microscopic Observations:* The specimen consisted of tumor tissue adjacent to fairly normal brain tissue. The tumor comprised islets of epithelial cells arranged in acinous or papillomatous forms separated by a fairly abundant loose stroma. The epithelial cells were uniform in size. The cytoplasm stained a deep pink color, the nucleus being round or oval, heavily chromatinized or vesiculated. Many acini showed a central blood vessel. The epithelial cells were arranged irregularly and to a variable thickness, causing the acini to depart considerably from its vascular connective tissue. In addition there were groups of epithelial cells which showed no particular arrangement. The stroma contained many cells which appeared to be cancer cells in various stages of degeneration. The nuclei especially were either pyknotic, undergoing rhexis or else had entirely disappeared. The cellular outlines were indistinct and the cytoplasm was slightly staining. While the tumor was well demarcated from the normal tissue, yet one could see at one part, invasion and at another an attempt toward fibrous encapsulation. The brain tissue, apart from some degenerative vascular changes with perivascular rarefaction showed no abnormality.

*Comment:* In this case, as in the previous one (Case 12) the cerebral metastasis in the absence of clinical evidence of cerebral involvement, must be regarded as having occurred as a terminal event.

*Case 14. Persistent productive cough of two years duration followed by progressive general weakness; terminal signs of focal cerebral involvement.*

*History:* (Adm. 485590; P.M. 12123). A man, aged 67 years, was said to have been subject to attacks of angina pectoris for about ten years. Two years before entering the hospital he became subject to persistent cough productive of blood-streaked sputum. With this he became gradually weak and during the last three weeks he was hardly able to walk because of generalized weakness.

*Examination:* The pupils were normal in outline and in reaction to light and in accommodation. The fundi were negative. There was generalized weakness, but it was most prominent in the left arm. The tongue deviated to the left. The deep reflexes were more active on the left side with the abdominal reflexes absent on that side. There was a Hoffman sign on the left side and an inconstant Babinski sign on the same side. General physical examination disclosed displacement of the trachea to the right. Dullness and diminished breath sounds over the left upper lobe were heard anteriorly and posteriorly. There was some clubbing of the fingers and toes.

*Laboratory Data:* Urine, blood cytology, serology and chemistry were normal. Sedimentation time was 35 minutes. X-ray examination of the chest showed an area of lobulated density in the upper lobe of the left lung, giving the appearance of a neoplasm. Lung puncture yielded tissue diagnosed as anaplastic carcinoma. Lumbar puncture revealed an initial pressure of 110 mm. of water; normal dynamics; Pandy reaction, 4 plus; total protein, 176 mg. per cent. Electroencephalogram was interpreted as indicating an infiltrating tumor of the right temporo-parietal region.

*Course:* The patient's condition declined gradually. He became markedly disoriented and somnolent, lapsed into stupor and died at the end of one month in the hospital.

*Necropsy Findings. General:* Peripheral carcinoma of upper lobe of the left lung with transpleural extension to chest wall. Pulmonary edema and congestion. Apical scar of left lung. Acute coronary occlusion; severe coronary arteriosclerosis; hypertrophy of both ventricles of the heart; generalized fibrosis of myocardium; acute infectious splenitis; chronic passive congestion of the liver; arteriolar sclerosis of the kidney; cystitis; chronic peptic ulcer of duodenum.

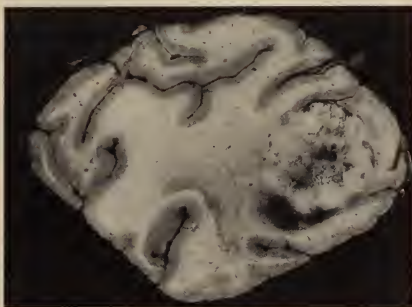


FIG. 12. Section of the right occipital lobe showing the relative size and appearance of the metastatic nodule (Case 14).

*Brain:* The right hemisphere contained a tumor in the region of the occipital lobe. It was spherical in outline, greyish pink in color, granular on the cut surface, and well demarcated from the adjacent tissue (fig. 12).

*Microscopic Observations:* A section through the tumor mass in the right occipital lobe, stained with hematoxylin and eosin, revealed a collection of densely packed tumor cells lining numerous villi and alveoli which had a fibrous tissue core containing a moderate number of thin walled blood vessels. On the surface of the villi and alveoli the tumor cells formed a lining which was several cells deep; some of the cells had a columnar appearance, especially those adjacent to the fibrous tissue cores; there was also a tendency for the cells to be arranged in rows. The tumor cells were large and had large nuclei with dense nucleoli; the cytoplasm was rather pale. Numerous mitotic figures were present. Within the tumor mass there were several large areas of necrosis in which there were collections of polymorphonuclear leucocytes. There was a sharp line of demarcation between the tumor mass and the adjacent brain tissue. At the border between the two there was an increase in the number of glial cells and the nerve cells in the adjacent areas showed degenerative changes, such as chromatolysis and shrinkage of the cytoplasm.

*Comment:* Of note in this case is the late appearance of signs pointing to the metastatic implication of the brain.

*Case 15. Sudden onset of symptoms pointing to focal cerebral disease; Jacksonian seizures followed by signs of increased intracranial tension and evidence of pulmonary disease.*

*History:* (Adm. 494467; P.M. 12269). A man, aged 50 years, twenty-three days before admission to the hospital, noted a feeling of fatigue in his left hand. He lacked his usual dexterity in playing the piano. The weakness progressed so that he was unable to move his left upper extremity. At the same time he began to drag his left leg and shortly thereafter he began to show emotional instability. He was sent to another hospital where it was noted on two occasions that his left arm and leg would twitch for periods of 2-3 minutes, there being no loss of consciousness. He then began to vomit repeatedly after meals and began to complain of mild dull headache in the right temporal region. He gradually became drowsy and dysarthric.

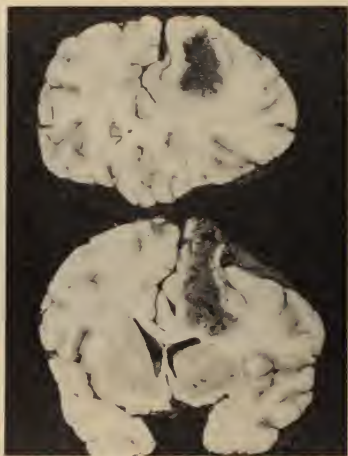


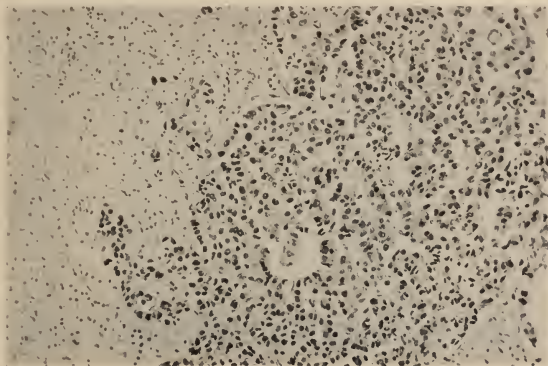
FIG. 13. Coronal sections of the brain showing the collapsed cyst-like metastatic lesion in the right cerebral hemisphere (Case 15).

*Examination:* The patient was drowsy, did not carry out commands correctly; the right pupil and palpebral fissure were smaller than the left; there was a central facial paralysis with complete left hemiplegia with corresponding pyramidal tract signs. Impairment of vibration and stereognostic sense were present on the left side. There were *diminished breath sounds and impaired resonance over the base of the right lung*. The blood pressure was 126 systolic and 86 diastolic.

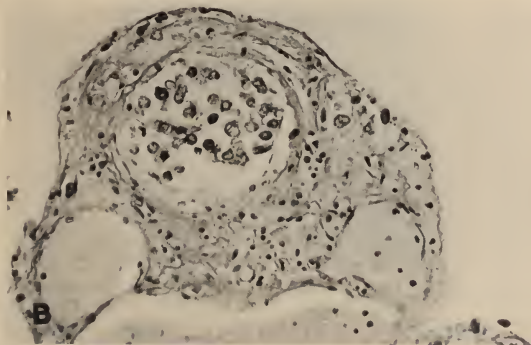
*Laboratory Data:* The cerebrospinal fluid was under an initial pressure of 200 mm. of water; except for a slight elevation of the total protein (72 mg. per cent) it was negative in all phases. Electroencephalography indicated the presence of an infiltrating tumor on the right side occupying the right frontal lobe, spreading toward the right parietal and temporal region. *X-ray examination of the chest revealed a circumscribed, sharply demarcated shadow in the right lung, diagnosed as a primary carcinoma.*

*Course:* In view of the x-ray findings a diagnosis of metastatic brain tumor was made. No operation was undertaken. The patient declined progressively and died on the seventh day in the hospital.

*Necropsy Findings. General:* Squamous cell carcinoma lower lobe of the right lung (peripheral type); metastases to the left lung, peritracheal nodes, liver; acute broncho-



A



B

FIG. 14 A. Histologic appearance of the metastatic lesion (Case 15) ( $\times 120$ ).

B. A blood vessel in the metastatic lesion exhibiting tumor cells in its lumen ( $\times 250$ ).

pneumonia; pulmonary edema and congestion; bilateral localized cortical hyperplasia of adrenals; acute congestion of spleen; cortical cyst of left kidney; atherosclerosis of coronary arteries without narrowing of aorta; benign polyp of sigmoid loop.

*Brain:* A cavity, the size of a golf ball, was found in the caudal portion of the right superior frontal gyrus. It was lined by ragged necrotic tissue and had a small opening at a point where it was separated from the dura. On sectioning the brain a reddish, soft, fairly

well circumscribed granular mass was found in the right cerebral hemisphere in the white matter subjacent to the superior frontal gyrus (fig. 13). Its rostral border was at the level of the genu of the corpus callosum and it extended caudally to the level of the tuber cinereum. It was circular in outline and at the point of its greatest expansion it was 4 cm. in diameter. The ventricular system was pushed over to the left and the right lateral ventricle was distorted, its lateral dorsal portion being pushed ventrally.

*Microscopic Observations:* Sections at the level of the tumor mass stained with hematoxylin and eosin showed it to form a fairly wide zone of neoplastic tissue encircling an area of brain disorganization. This zone was sharply demarcated from the adjacent brain tissue (fig. 14A). The tumor tissue was rich in cells. The latter were of the cuboidal or low columnar type. It formed large encircling zones around blood vessels. What was still more significant was the presence of tumor cells within the lumen of an occasional blood vessel (fig. 14B).

*Comment:* This case offered practically no diagnostic difficulties as to the identification and localization of the cerebral lesion. Of great significance was the discovery of neoplastic cells within some blood vessels in regions of metastatic cerebral lesions. It indicated that the blood stream served as the distributor and conveyor of the carcinomatous material to the brain.

*Case 16. Asthmatic attacks of two years duration followed one and a half years later by the development of cerebral manifestations, first general and later localizing in character; x-ray studies disclosed pulmonary mass and pathologic fracture of the eighth rib; left frontal lobe tumor diagnosed; craniotomy; parts of tumor removed, reported as metastatic carcinoma.*

*History:* (Adm. 358046; P.M. 8981). M. W., aged 44, two years before his admission to the hospital, became subject to periodic attacks of asthma. In one of such attacks, six months before entering the hospital he lost consciousness for about  $\frac{1}{2}$  hour and on one occasion had an hemoptysis. As time went on he became depressed, emotionally unstable and disinterested, developed a tremor of the right hand and became subject to daily non-projectile vomiting. He lost 30 pounds in the course of four months.

*Examination:* The patient was euphoric, disoriented and incoherent. There was left supranuclear facial weakness, mild right hemiparesis and right hyperreflexia. There were localized clonic movements of the left upper extremity without loss of consciousness.

*Laboratory Data:* Blood and cerebrospinal fluid studies were negative in all phases. X-ray examination disclosed a pathologic fracture of the eighth rib and a *circular mass at the root of the left lung posteriorly*; also one at the root of the right neck in the region of the thyroid gland, displacing the trachea.

*Course:* A diagnosis of left frontal lobe brain tumor was made. While under observation he developed papilledema, weakness in the right upper extremity became more marked, and he became more drowsy. A craniotomy was performed and parts of the tumor were removed from the pre-rolandic area. Material for histopathologic study was reported as metastatic in character. Following the operation the patient developed pneumonia and died sixteen days later.

*Necropsy Findings. General:* Carcinoma of the postero-lateral branch of the left lower lobe bronchus with extension to regional lymph nodes, both adrenals, and brain. Chronic and acute bronchitis and bronchiectasis; suppurative confluent bronchopneumonia; dilatation of right ventricle of heart; pulmonary emphysema and edema; chronic cardiovascular disease; chronic cholecystitis and cholelithiasis.

*Brain:* In a series of coronal sections the following was revealed: Section at the level of

the genu of the corpus callosum showed four large tumor masses, two in each hemisphere. In the left hemisphere, one was small, near the dorsomedial border and measured about  $1\frac{1}{2}$  cm. in diameter, it was soft and grayish in color; the second, the large one occupied almost the entire depth of the hemisphere and involved the two upper frontal convolutions (fig. 15). This mass was markedly hemorrhagic and somewhat firmer in consistency. In the right hemisphere a large excavated tumor mass was found at about the same relative location as the larger one in the left hemisphere. It had the appearance of a cavity filled with necrotic tissue and surrounded by softened tumor tissue. A similar mass was found in the inferior

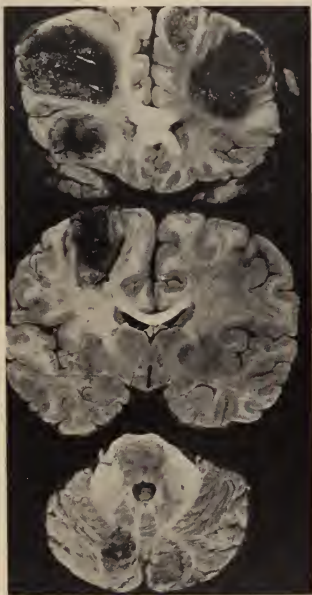


FIG. 15. Coronal sections of the brain showing appearance and distribution of metastatic tumors (Case 16).

portion of the right frontal lobe, and measured about 2 cm. in diameter. All these masses extended in their antero-posterior plane for a distance of about 2-5 cm. Another mass measuring  $1\frac{1}{2} \times 3$  cm. was found in the right parietal lobe. Two smaller masses were found in the cerebellar hemispheres near the posterior notch. They were circular, well demarcated, and limited to the cortex.

*Microscopic Observations:* Sections stained with hematoxylin and eosin revealed an infiltrating tumor which was degenerated and necrotic in the center (fig. 16). The tumor was composed of round and oval cells with vesicular nuclei arranged in rosettes or radiating from blood vessels. Mitotic figures and an occasional giant cell were seen.

*Comment:* It is difficult to find sufficient ground for the exploratory craniotomy in this case, since the metastatic character of the lesion could hardly be dismissed as most probable and its dissemination as later disclosed at necropsy could be predicted.

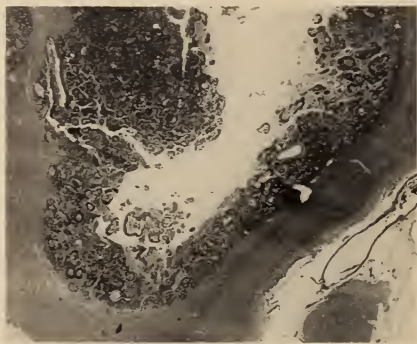


FIG. 16. Histologic appearance of metastatic lesion (Case 16) ( $\times 7$ )

*Case 17. Acute onset of cerebral manifestations, followed by development of signs of intracranial tension; focal signs meager; diagnosis of brain tumor; its metastatic character suspected; rapid decline; death; necropsy, multiple metastatic carcinoma of the brain.*

*History:* (Adm. 288563; P.M. 6119). A. F., a man, aged 55 years, dated the beginning of his illness to three months before his admission to the hospital, the onset being marked by an unusually long period (thirty-six hours) of sound, uninterrupted sleep. It was followed by pain in the right arm and hand. Infected teeth were extracted in the belief that they were the cause of his pain. Two weeks after the onset of the pain severe headaches set in, followed shortly by progressive impairment of vision. About the same time his memory began to fail.

*Examination:* The patient was confused and disoriented. There was slight blurring of the discs. The pupils were unequal and irregular, the right pupil reacting sluggishly to light and in accommodation. There was weakness of the left side of the face of a central type. All the extremities were spastic, those on the left side being weaker than those on the right. The left upper extremity was held in a position of semiflexion at the elbow. The deep reflexes on the left side were hyperactive; the abdominal reflexes were depressed. There was moderate rigidity of the neck and a Kernig sign was elicited.

*Laboratory Data:* The cerebrospinal fluid was under slightly increased pressure. It was clear, free of cells and otherwise normal. All other laboratory studies gave normal results.

*Course:* A diagnosis of cerebral neoplasm was made, but the location of the tumor was in doubt. As hoarseness developed and the patient experienced difficulty in swallowing, it was thought advisable to look for probable malignancy elsewhere. X-ray examination of the chest revealed an oval shadow 4 inches in diameter, occupying the middle third of the

right side of the chest, which was thought to be a neoplasm. The patient's condition declined rapidly and he died on the eighth day in the hospital.

*Necropsy Findings. General:* Primary carcinoma in the lower lobe of the right lung.

*Brain:* On the inferior surface of the right temporal lobe was a circular area about 3.5 cm. in diameter which was distinctly harder to palpation than the surrounding cerebral tissue. Coronal sections of the brain revealed a large tumor in the right temporal lobe; it was 4 cm. in diameter and reached the inferior surface of the right temporal lobe. On the lateral side of the mass was a thin layer of cortical and subcortical tissue; medially the tumor encroached on and compressed the right thalamus. The ventricular system was distorted, the body of the right lateral ventricle being compressed and the left slightly dilated. A second tumor, measuring 1 x 1.5 cm. was located in the superior frontal gyrus of the right cerebral hemisphere; it reached the pia-arachnoid in the dorsomedian fissure. A third tumor, measuring 1 cm. in diameter, was observed in the superior parietal gyrus of the left cerebral hemisphere; it reached the surface of the dorsomedian border of the hemisphere. The tumors were well delimited from the adjacent cerebral tissue. They were similar in gross appearance; the surface was rough, pale gray and interrupted by dark hemorrhagic areas and numerous small cyst-like spaces.

*Microscopic Observations:* The tumor tissue was for the most part necrotic, especially those portions at the greatest distance from blood vessels. The neoplastic cells which were found as island surrounded by necrotic tissue displayed a variety of shapes and sizes; they were predominantly round or oval; some were very large. Similarly, the nuclei varied greatly in size; all were lightly reticulated. There was a tendency in places toward the formation of acini, and in these areas the cells tended to be columnar or cuboidal, with the nucleus at the base of the cell. In one area the tumor cells had invaded the leptomeninges. On the whole, there was a distinct line of demarcation between the tumor and the adjacent brain tissue. In some places, however, small groups of neoplastic cells strayed away from the main tumor mass into surrounding tissue.

*Comment:* The development of signs pointing to involvement of parts of the nervous system other than the cerebral hemispheres drew attention to the probability of dissemination of the neoplastic process, and hence to its probable metastatic character. This interpretation, in turn, was supported by the roentgenologic signs in the chest suggesting the presence of a mass, which was thought to be neoplastic. The subsequent course and the post-mortem observations fully verified this diagnosis.

*Case 18. Signs and symptoms of pulmonary involvement of three months duration; sudden onset of cerebral manifestations; rapid decline and sudden death.*

*History:* (Adm. 338780; P.M. 8328). A. D., a man, aged 49 years, was subject to headache and epigastric pain for about three years and to chest pain and cough for three months before his admission to the hospital. In the course of this time he lost 38 pounds and more recently became exceedingly weak, unable to walk.

*Examination:* The positive neurologic findings included transient diplopia on straight gaze; occasional nystagmoid jerks on lateral gaze. The fundi were normal. The patient was stuporous, markedly emaciated, and subject to cough productive of greenish-yellow sputum.

*Laboratory Data:* X-ray examination of the chest indicated the presence of carcinoma of the lung. All other tests except for a moderate leucocytosis were within normal limits.

*Course:* The patient complained of vertigo and would vomit on turning the head to the left. This suggested the possibility of a metastatic lesion in the region of the fourth ventricle. His condition declined rapidly and he died rather suddenly.

*Necropsy Findings. General:* Primary carcinoma of the main right upper lobe bronchus with metastases to regional lymph nodes and both adrenals; carcinomatous lymphangitic infiltration with secondary infection of the right upper lobe; bullous emphysema of both lungs; healed duodenal ulcer; brown atrophy of the heart and liver.

*Brain:* On sectioning the brain a large excavation was found in the left parietal lobe extending forward to approximately the level of the anterior commissure. It measured 5 x 3 cm., was filled with a sanguinous material and was lined by softened eroded material. In the cerebellum another defect was found in the white matter (fig. 17). It was globoid in outline and measured 2 x 2½ cm. It was filled with a brownish gray liquid material and part of its wall showed an area of discoloration measuring about ½ cm. in depth, giving the impression of metastatic material. Another small area was found on the opposite side in



FIG. 17. Coronal sections of the brain showing metastatic lesions in cerebrum and cerebellum (Case 18).

the region of the dentate nucleus and its periphery. It was filled with caseating material and surrounded by a distinct zone of neoplastic tissue.

*Microscopic:* Sections of the cerebrum and cerebellum both show a circumscribed area of closely packed large polyhedral cells growing among new formed capillaries with evidence of central necrosis and in some places assuming a cord-like arrangement. Many mitotic figures were seen.

*Comment:* Little need be said about this case except that the clinical manifestations which suggested a lesion about the fourth ventricle were substantiated by the necropsy observations.

#### SUMMARY AND GENERAL COMMENT

This article is mainly a record of the clinical manifestations and anatomical features of thoroughly investigated cases of bronchogenic tumors with metastasis

to the brain. Only a few conclusions are drawn and only such which are warranted by authenticated observations. With this in mind 18 were selected from a total number of 58 cases of metastatic brain tumor studied on the several services of The Mount Sinai Hospital. The cases chosen were those in which a full post-mortem examination disclosed the lungs to be the seat of the primary carcinomatous growth.

A review of the clinical histories disclosed that only in 2 cases were there no apparent pulmonary symptoms or signs throughout almost the entire clinical course and in 2 cases pulmonary signs made their appearance after the development of cerebral manifestations. In 7 cases pulmonary signs were already present in the early clinical course, but were not confirmed by x-ray examination, while in 7 other cases, such signs and symptoms preceded the development of cerebral manifestations and were confirmed by x-ray studies of the chest.

The absence of signs and symptoms referable to the chest during the period preceding the development of cerebral dysfunction is, of course, a disturbing feature which creates diagnostic difficulties. On the other hand, it is quite obvious that the presence of such signs or symptoms, no matter how mild and doubtful, should not be dismissed as insignificant without being investigated by every available means in almost every case of suspected expanding intracranial lesion before a bronchogenic carcinoma is excluded as its probable source of origin.

The imperative need of x-ray studies of the chest under such circumstances becomes more obvious as greater recognition is given to malignant pulmonary neoplasms as a frequent source of metastasis to the brain. It is equally important to bear in mind that the lung often, as it intercepts a malignant process, establishes itself as a metastatic focus and in turn as a source for metastasis to the brain. Hence, the logical conclusion is that in every instance of suspected brain tumor in patients in or above the fourth decade of life, x-ray examination of the chest should be carried out as a routine procedure.

The mode of onset of the cerebral manifestations, as was already pointed out elsewhere (1) is quite typical, if not always pathognomonic, of metastatic tumors of the brain. A more or less abrupt appearance of manifestations of cerebral involvement, particularly the development of intense headache, mental changes, Jacksonian seizures followed by more definite and measurable signs of increased intracranial pressure (papilledema, elevated pressure of the cerebrospinal fluid) and by objective signs pointing to dissemination of the lesion, should arouse a strong suspicion of the metastatic character of the expanding intracranial lesion. This is particularly true when subsequent events in the unfolding clinical picture maintain a similarly rapid *tempo*.

Attention has already been drawn to the observation that metastasis to the brain, arising in a wide variety of primary sources, for some unexplained reason, is more common among males. It was suggested that this situation could be explained in part by the fact that the investigated material was drawn from services which care for few patients with breast malignancy. But apparently this is not the only and dominant reason, as this disproportion in sex incidence is found even still more striking in this study of a single category of verified metastatic bronchogenic tumors. Here the incidence of metastases to the brain is still

higher for males; out of a total of 18 cases, 3 were in females. This is in conformity with the observations of Dr. Paul Klemperer (personal communication) that bronchus carcinoma is far more frequent in males than in females.

Analyzing the age incidence it is found that only one case was encountered in the fourth decade of life, while the fifth decade numbers 8 cases, the sixth 5 cases and the seventh 4 cases. This curve speaks for itself and when compared with that of the aforementioned larger group of metastatic brain tumors, it discloses a very low incidence of metastasis of bronchogenic neoplasms in the fourth decade and none at all below this age level; it maintains high levels during the sixth and the seventh decades of life, tapering off from then on.

In this series of bronchogenic brain tumors, as in the larger group previously reported in which there were several sources of origin, including that of the lung area, there is a slight change in the ratio between solitary and multiple metastases in the brain, the incidence of multiple lesions rising from 52 per cent in the previous series to 67 per cent in the present series of cases.

Not without significance also is the observation that in the instances in which the metastatic lesion in the brain was a single one, metastases to other organs or other parts of the body were more or less limited and were found in only three out of seven cases, while in the instances of multiple foci of metastasis to the brain, widespread metastases to other parts of the body was found in 9 out of 11 cases.

In view of the fairly frequent occurrence of solitary metastatic tumors in the brain, it has been pointed out (1) that an occasional metastatic brain neoplasm yields to surgical interference, and similarly it is said (5) that in an occasional instance of bronchogenic metastatic cerebral tumor surgical intervention offers some promise for a longer survival period. The results obtained from such treatment of metastatic tumors in a few cases of the herein reported series does not justify such hopes.

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# THE INFLUENCE OF NEURO-HORMONAL REGULATIONS ON ANAPHYLAXIS AND ALLERGY

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Anaphylaxis as seen in the lower animals serves as the prototype of allergy in the human being. While both the allergic as well as the anaphylactic state may be induced in man, its so-called spontaneous appearance has been attributed to constitutional and hereditary factors. Many theories have been advanced in explanation of the underlying nature of the constitutional predisposition to the allergic state. Some deal with the influence of the endocrine glands, others with the vegetative nervous system, while still others with psychologic factors and probable biochemical changes resulting therefrom.

The proponents of the endocrine theory find support for their views in the appearance or disappearance of various allergic manifestations at certain periods of life such as puberty, menstruation, pregnancy and the menopause, the marked relief from adrenalin in controlling allergic phenomena, and the tendency to hypotension and hypoglycemia, suggestive of adrenal insufficiency. Additional evidence in favor of these hypotheses were looked for in the effects of extirpation of the several glands of internal secretion and the reinjection of their products on sensitization. The results of these experiments are as follows:

## A. INHIBITION IN ANAPHYLAXIS

1) It has been shown by Kepinow (1) that inhibition of anaphylactic shock may be brought about in guinea pigs which had been subjected to thyroidectomy. The blood serum of such animals does not contain any anaphylactic antibodies utilizable for passive transfer. In dogs, Houssay and Cisneros (2) also noted diminished anaphylactic reactivity following thyroidectomy.

2) Thyroidectomized guinea pigs may again be sensitized after feeding with thyroid extract. If thyroidectomy however is performed before the sensitizing injection, guinea pigs are usually protected against fatal anaphylactic shock, although some symptoms like dyspnea and hypothermia may occur. Nevertheless, if large doses of antigen are introduced, thyroidectomy does not protect the animal against shock (3). Moreover, animals can be rendered passively sensitive provided they are injected with serum from previously sensitized *normal* animals. Such results, despite thyroidectomy point to the inherently independent character of the cellular response.

3) Thyro-orchidectomy markedly lessens anaphylactic shock.

4) Parathyroid removal causes a striking diminution in anaphylaxis.

5) Injection of adrenalin prior to the injection of the shocking dose diminishes anaphylactic susceptibility.

6) Thymectomy according to Yun (4) causes a moderate inhibitive effect on anaphylaxis.

7) Anterior pituitary extract in large doses, gonadotropic hormone and preg-

nancy urine extract, injected into male guinea pigs markedly diminish anaphylactic shock.

8) Orchidectomy in rabbits has a marked inhibitive effect.

9) According to Lumiere and Couturier (5) pregnant guinea pigs are almost entirely resistant to anaphylactic shock.

#### B. ACCELERATION OF ANAPHYLAXIS

1) The enhancement of the anaphylactic reaction may be induced by experimental hyperthyroidism through the use of thyroxin. Salomonica and Kurzrock (6) claim that this effect can be neutralized by the injection of anterior pituitary-like extract. After two or three weeks of administration of chorionic gonadotropin the basal metabolism returns to normal in such animals. Continued administration of this extract has a depressing effect on anaphylaxis which becomes more significant if introduced prior to sensitization of the animal rather than after.

2) Ovariectomy causes a mildly aggravating effect on anaphylaxis.

3) Hypophysectomy, according to Molomut (7) brings about increased susceptibility to fatal anaphylactic shock in male rats (65 to 75 days old), who received the shocking reinjection 47 days after operation.

4) Injection of pancreatic substance and insulin, as recorded by Hajos (8), likewise increase the susceptibility to anaphylactic shock.

5) Adrenalectomy in rats causes an increased susceptibility to anaphylaxis. Prolonged injection of adrenalin, however, may also cause an increased susceptibility according to Horster (9).

The aforementioned investigations indicate that inhibition of anaphylaxis may be induced in the lower animals by removal of the thyroid, parathyroid, testicles, thymus; or the injection of adrenalin, anterior pituitary-like extracts, gonadotropic hormone, pregnancy urine extract, as well as by the state of pregnancy itself. Acceleration of anaphylactic shock is promoted by hyperthyroidism, ovariectomy, hypophysectomy, adrenalectomy in rats, and injection of pancreatic substance and insulin.

On reviewing this experimental data it seems that the conclusions reached by some workers in this field are too generalized and are based on insufficiently controlled findings to make it possible to accept them without further proof. With the exception of the results in thyroidectomy where inhibition of anaphylaxis is associated with a depression of the sensitizing or precipitating antibodies, the mechanism involved in the ablations of the various other endocrine glands is not clear. With the extirpation of important organs like the hypophysis, so many changes in the defense mechanism ensue that it is difficult to identify any specific role that the elimination of this gland plays in anaphylaxis.

Opposed to the proponents of the endocrine theory are those who maintain that the allergic state is transmitted as a Mendelian dominant character. This inherited factor, although its nature is not definitely known, is manifest in the susceptibility of the tissue cells of the offspring of allergic parents to become sensitized on contact with specific antigens.

Phylogenetically the cells of the body take precedence over the hormonal system, hence their individual functions antedate any influence on the part of the endocrine glands. Experimental evidence for this has been adduced by Netter and Witebsky (10), who demonstrated anaphylaxis in the vascular system of the three day old chick, by the addition of "normal rabbit type sera" and Forssman antisera, before any endocrines or nerves are developed. Tests with atropine, epinephrine, ergotamine and acetylcholine which are known to affect the autonomic nervous system proved ineffective when applied to the chick embryo at this stage of life, thus proving the non-existence of neurogenic structures.

The Shultz-Dale reaction on the excised sensitized uterus is another example of the cellular nature of anaphylaxis.

Shwartzman (11) *in vitro* experiments was able to give further support to the cellular nature of allergy. By the addition of tuberculin, he demonstrated tuberculin hypersensitiveness in explanted mononuclear leucocytes derived from tuberculous animals grown according to the Carell technique.

Clinically it has been shown by Naegli de Quervain *et al.* (12) that transplantation of sensitized skin grafts on normal individuals yields specific reactions limited to the passively transferred fragment of tissue, after exposure to the specific allergen.

As growth proceeds however, whether in the developing chick or human embryo, the tissue cells become infiltrated by neurogenic elements. With the development of the endocrine system, vast integrations take place between the vegetative nervous system and the hormones on the one hand, and the tissues on the other, which harness without effecting the fundamental autonomy of the individual cells. This is well demonstrated by the following group of patients in whom the thyroid, thymus and parathyroid glands were involved.

### *Thyroid.*

*Case 1.* B. E., aged 36 years, presented typical symptoms of hyperthyroidism in 1936. She had exophthalmos, tachycardia, loss of weight, tremor, sweating, diarrhea and a basal metabolic rate of plus 55. When she came to the allergy clinic in February 1939 she had marked symptoms of Graves' disease with a basal metabolic rate of plus 71. She complained of having had hay fever for two years. While being referred to the allergy clinic she was also advised to be operated on for hyperthyroidism. She ignored both recommendations. She was found to be highly sensitive to ragweed pollen extracts so that it was necessary to increase her immunizing dose very cautiously. She nevertheless responded well to this treatment. Whether this heightened susceptibility to the pollen extracts was due to the hyperactivity of the thyroid is difficult to say. Cases in which hyperthyroidism obviously does not exist and yet display a similar high degree of sensitiveness to pollen are not infrequent.

*Case 2.* E. F., aged 45 years, gave a family history of asthma and hay fever. She presented signs of Graves' disease and was subject to urticaria and ragweed hay fever with cough for eight years. Her basal metabolic rate recorded in December 1938 was plus 58. She had tachycardia, tremor, loss of weight, but no exophthalmos. At one time she had auricular fibrillation. On admission to the allergy clinic the manifestations of the Graves' disease were under complete control as a result of a subtotal thyroidectomy. She was immunized against ragweed pollen and developed full protection. With the omission of ragweed inoculation the symptoms returned. Her skin reaction to ragweed remained marked.

*Case 3.* A. R., aged 36 years, had symptoms typical of Graves' disease in 1937 with a basal metabolic rate of plus 44. She had been a hay fever sufferer for seventeen years. In June 1937 she had undergone a subtotal thyroidectomy. Her basal metabolic rate dropped and remained minus 4. She first came to the allergy clinic for treatment in May 1939. Following immunization symptoms of hay fever have diminished 75 per cent.

Cases 1, 2 and 3 illustrate above all that the allergic manifestations prevailed independently of hypothyroidism; secondly, removal of the thyroid did not influence the fundamental disease; thirdly, immunization may be successfully carried out even in the presence of hyper- and hypothyroidism.

#### *Thymus.*

The older clinicians thinking in terms of morphologic pathology accepted the presence of an enlarged thymus as a cause of asthma without closely investigating whether the wheezing respiration was due to mechanical obstruction of the trachea, or to the existence of hypersensitiveness, hence the term "thymic asthma" came into usage. Given an enlarged thymus the question arises whether the wheezing is the result of obstruction caused by the affected gland, is it dependent upon some secretory activity of the thymus or determined by the presence of hypersensitiveness to various foreign proteins. According to Waldbott (13) many children with enlarged thymus have proved to be cases of true hypersensitiveness with the thymus gland playing no role in the causation of the asthma. Yun, however, reports that thymectomy in animals inhibits sensitization, thus implying that the thymus is in some way implicated in the allergic process. The following case clearly demonstrates that the thymus gland probably has no influence on asthma caused primarily by protein hypersensitiveness.

Patient B., 5 years of age, was suspected at birth of having an enlarged thymus because of difficulty in breathing. X-ray examination confirmed this diagnosis and radium therapy was instituted. The thymus disappeared completely. At the age of four, while in the country, the child developed ragweed hay fever followed by bronchial asthma, although the thymus, that is to say the enlarged mediastinal shadow found on x-ray examination was no longer present. The child is still suffering from asthma due to pollen sensitization.

#### *Parathyroid.*

Parathyroidectomy is assumed to have an inhibitory influence on experimentally induced anaphylaxis according to Yun (4). It has not been found to have this effect clinically in the following case.

Patient C., aged 46 years, with a family history of asthma was first seen by me in January 1937. He was subject to asthmatic attacks since October 1910, and had urticaria in 1912. The asthma had become perennial during the past twenty years. The causative factors were found to be multiple sensitivity to various inhalants, foods and bacteria. The asthmatic seizures were relieved by adrenalin and morphine. In 1935 he developed a number of symptoms suggestive of hyperparathyroidism associated with disturbed renal function. He went to the Mayo Clinic where the diagnosis was confirmed, and he was operated on for a parathyroid tumor in November 1935. Following the operation the asthmatic manifestations became more severe even though his blood calcium persisted at a high level of normal, 11 mg. per cent. This is significant inasmuch as it is often claimed that intravenous administration of calcium controls asthmatic attacks. He refused to follow a prescribed diet and proper immunization but went to Florida instead where his symptoms persisted and became worse because of the constant presence of pollen. In 1940 he went to Johns Hopkins

Hospital where he was found to have, in addition to asthma, manifestations of arteriosclerosis with hypertension, marked retinal changes and grave renal insufficiency. He died suddenly in what appeared to be cardiac failure. At autopsy a dissecting aneurysm extending from the sinus of Valsalva to the renal pedicle was found.

These cases emphasize the inherent nature of the cellular reactions in hypersensitive states irrespective of endocrinal influences. But in contrast to the aforementioned observations there are many cases with and without a typical history of allergy in whom symptoms begin during a critical period of development such as puberty and menstruation or may become aggravated by menstruation. There are other patients whose symptoms cease or just appear with the onset of pregnancy or climacterium. Farmer (14) recently described a series of cases which fall into this category. He records two patients, aged 26 and 37, suffering with severe angio-neurotic edema and urticaria whose symptoms first appeared shortly after pregnancy, and three patients aged 34, 29 and 20 respectively, whose hay fever and asthma disappeared during pregnancy. He also described two patients aged 49 and 48 with vaso-motor rhinitis and angio-neurotic edema, which first became evident during the climacterium. One of these patients who gave negative skin reactions to various allergens became markedly improved on estrogenic therapy. Two other patients, one aged 54 approaching her menopause but still menstruating and the other aged 37 with irregular menstruation, who manifested urticaria and severe angio-neurotic edema, also were improved following estrogenic therapy. Both of these patients reacted negatively to skin tests.

Waldbott and Bailey (15) determined the blood estrogens by the method of Frank and Goldberger (16) in 79 female patients with pre-menstrual asthma, and found a relative estrogen deficiency in 63.3 per cent as compared with 4.7 per cent in a control group of 42 non-allergic women. Premenstrual administration of large doses of theelin and lipolutin, however, were found to be of benefit only in a limited number of the patients who had symptoms exclusively before and during menstruation. Uhrbach (17) describes a case of dermatitis with dysmenorrhea in which no estrogens were demonstrable in the urine. In his patient no benefit was obtained from estrogenic therapy. Interruption of the cyclic ovarian activity, however, first in the course of pregnancy and later by x-ray therapy resulted in improvement of the dermatitis. On the other hand, Drips and Brunsting (18) described a case of urticaria with menstrual irregularity in which estrogens were absent from the urine and in which estrogenic therapy proved beneficial.

It seems apparent from these reports that the anterior pituitary or the gonads may act by enhancing or inhibiting manifestations of allergy. It is difficult however to understand why estrogenic therapy should be effective in some cases and not in others. Is it possible that in those instances in which estrogens are of value, the presenting symptoms although resembling allergic phenomena are really not due to allergy at all but are in some obscure manner the results of disturbed cellular metabolism giving rise to reactions simulating immune processes, in which the autonomic system might also participate subject to hormonal regulation? An examination of the underlying factors involved in the immune reaction associated with hypersensitiveness and those responsible for cellular

reactions simulating allergy, discloses the following. The immune response is mediated by an antigen-antibody interaction on or within the cell which is supposed to release H. substance. This leads to increased capillary permeability and edema, and accounts for the clinical manifestations of asthma or urticarial wheal. The non-immune cellular reaction resembling the allergic response which may also lead to the development of urticaria or wheezing respiration in man as well as in animals, may be induced by iontophoresis or intracutaneous injection of histamine, pilocarpine or acetylcholine as has been demonstrated by Lewis (19), Grant, Pearson and Comeau (20), Hopkins, Kesten and Hazel (21), Ewert and Kallos (22) and others. Ewert and Kallos produced both asthma and electrocardiographic changes in guinea pigs following inhalation of finely divided histamine and acetylcholine similar to those described by Harkavy and Romanoff (23) in allergic individuals.

Grant, Pearson and Comeau in their studies of urticaria provoked by physical agents such as heat, cold and emotional stimuli in six subjects, came to the conclusion that such urticaria is dependent upon central stimulation by impulses passing through the efferent peripheral nerves which liberate acetylcholin or substances very closely related to acetylcholin in their pharmacologic effects. The acetylcholin thus set free as a result of stimulation of cholinergic nerve fibres, leads to the release of H. substance from the skin, responsible for the urticaria. They found support for this concept in the fact that blocking of a cutaneous nerve prevents in its area of distribution, the development of the urticaria following the application of heat. These observations suggest that in addition to the immunologic processes there is also a nervous mechanism which may set up chain reactions releasing H. substance, not only in the skin but probably also in the mucous membrane of the respiratory tract. Locally this H. substance may be liberated through a system of nerves which Lewis designated as the nocifensor. Alexander (24) in his discussion of "Allergic Syndromes in the Absence of Allergens" speculates upon the possibility that the nocifensor system of nerves by elaborating histamine-like substances may be responsible for non-allergic vaso-motor rhinitis and possibly for some types of so-called intrinsic bronchial asthma for which evidence of an underlying immune process is still lacking. If the concept that nervous stimuli of cholinergic origin may be responsible for the release of H. substance in the skin leading to reactions similar to those induced by immune processes is accepted, it is necessary also to consider the possibility that the adrenergic stimuli from the "sympathectonic" system may operate to counteract these effects. Although experimental proof for this is lacking the effective control of allergic, cholinergic, and histamine reactions, by adrenalin is generally recognized.

In the light of these observations and for the purposes of therapy it is important to distinguish the kind of excitation and the mechanism involved in a given instance. Cases which present symptoms such as asthma, urticaria, vaso-motor rhinitis based upon sensitization to foreign proteins should be separated from those dependent upon neurogenic stimuli of internal or external origin. The internal stimulation has two probable sources; the central nervous system, partic-

ularly the diencephalic region, the site of emotional interplay, and the closely related hormonal apparatus. Thence the stream of stimuli is conveyed by the autonomic nervous system to the receptive cells of the shock organs. The external excitants may be represented by physical agents such as cold or heat, often referred to as "physical allergy". There are cases, however, in which not only one, but multiple mechanisms may operate concurrently, and account for the persistence or exacerbation of allergic symptoms. In one of the patients the asthmatic seizures were the result of sensitivity to cold, heat, pollen, bacterial sensitization and emotional states. In another, a Puerto Rican patient, aged 29, attacks of asthma invariably coincided with the onset of pregnancy. The problem was whether the wheezing was due to sensitization by foreign proteins developed during the process of gestation, or disturbance of the vegetative nervous system resulting from the altered glandular state.

Finch (25) recently reported the successful treatment of hyperemesis gravidarum by desensitization with progestin on the basis of having found patients suffering with these symptoms sensitive to their own corpora lutea. If confirmed, this complicates the situation in that it suggests that immune as well as neurogenic reactions may be involved in such cases.

Whether the initiation or suppression of allergic manifestations during periods approximating specific endocrinal cycles are due to the direct influence of the endocrine glands which awaken latent susceptibilities of the cell to antigenic stimulation, or depress them, or whether this trigger mechanism is exercised by the autonomic nervous system under hormonal control, is not definitely known. That the autonomic nervous system is very probably involved, however, may be suggested by the fact that both these systems frequently act as a unit and that hyperactivity and suppression of cellular function are also properties of the cholinergic and adrenergic fibres. Their proper balance is most important for the well being of the patient. An illustration of what autonomic imbalance, caused by the menopausal state, may bring about, is shown by the following case:

A. C., a woman, aged 48 years, was successfully immunized for epidermophytosis in 1937. In 1938 with the onset of the menopause she became resistant to the same form of therapy because excessive generalized sweating, involving her feet as well, supervened. Estrogenic therapy reduced the hyperhidrosis and the patient's condition promptly yielded to the immunization successfully carried out in 1937.

In contrast to this, are the trophic disorders directly dependent on deficiency of certain endocrine glands as for example the thyroid in hypothyroidism. Here the skin is dry, the hair falls out and eczema as well as urticaria may develop. Therapy to be successful in such cases must not only be directed to the detection and removal of the exciting allergens but also to the insufficient hormone responsible for the alteration in the defense mechanisms of the affected tissues. In this connection it may be said that a great deal of care is to be exercised in the use of hormones in the treatment of disturbed endocrinal states. Not only toxic but also allergizing effects may follow in the allergic individual, and symptoms characterized by urticaria, angio-neurotic edema, eczema, asthma, gastro-intestinal symptoms, etc. may supervene. We have seen cases sensitized by the use of

thyroid extract with resulting urticaria. Instances of sensitization to anterior and posterior pituitary extracts, pancreatic and estrogenic hormones, as well as their vehicles such as sesame oil, have also been frequently reported. Insulin is a most common offender responsible for allergic symptoms. Reactions may follow spontaneously after the first injection of an endocrine product, indicating an inherent sensitivity to the hormone or it may be acquired after repeated injections of a particular substance. Here one must differentiate between allergy to the protein of the animal from which the gland product had been derived, such as beef or pork, and the protein of the hormone itself. In the case of insulin, numerous examples of sensitivity to the purified crystalline protein itself, have been demonstrated.

A review of these observations suggests that similar to the immune reaction, hormonal or neurogenic stimuli may be responsible for alterations in cellular responses. These changes may occur independently or in association with specific endocrinal cycles and are manifested in the direction of hyperactivity or under activity. In the case of hyperactivity, the reactions are referred to as "allergic" because they simulate allergy although they are not allergic in the immunologic sense. In the instance of underactivity or total lack of reactivity the term "anergy" is frequently employed. Whether the predominance of cholinergic or adrenergic stimuli depend upon the individual make-up, "vagotonics and sympathicotomics" in the sense of Eppinger and Hess, or based upon some type of "sensitivity" of the cholinergic or adrenergic systems *per se*, are questions which need further elucidation. That cells of neurogenic origin just as any other, are subject to sensitization is well established. Thus serum sensitization may be responsible for peripheral neuritis, etc. One cannot, however, dismiss the thought that there must be an inherent predisposition on the part of tissue cells in certain individuals towards hypersensitiveness before symptoms characteristic of allergy may develop. If that were not so, every individual should have urticaria or asthma as a result of allergenic, hormonal or neurogenic stimulation. This is clearly illustrated by the following case:

M. S., aged 24 years, was first seen in 1923 at the age of four years suffering since infancy with eczema and bronchial asthma. Investigation disclosed sensitivity to foods, pollens and inhalants. She disappeared from observation until 1943. On her return the following history was elicited. With the onset of menstruation at the age of thirteen all her symptoms disappeared. She ate and drank everything just as an average normal human being. The state of apparent immunity continued until the age of twenty when in the country during the month of June she began to sneeze and developed shortness of breath. This grew progressively worse and now at the age of twenty-four years she suffers from a recurrence of hay fever and perennial asthma.

It would seem therefore that the neuro-hormonal system may regulate but not initiate the hypersensitive type of cellular reaction. This control is limited, for as has been shown, in the cases where sensitization to specific allergens is fully developed, the neuro-endocrine regulatory function assumes a minor or an entirely negative role. In view of the multiplicity of factors involved in problems of allergy it is futile to champion the psychotherapeutic, endocrine, or any other

exclusive approach to the treatment of patients with allergic manifestations. Each possible element must be taken into account.

It appears to be justified to conclude from these considerations based upon laboratory and clinical findings, that allergy is due to a specific cellular reaction, the mechanism of which is to a certain extent understood. It seems likewise that the threshold of response can be influenced in the direction of hyper- or hypoactivity by many factors including hormonal, neurogenic as well as extrinsic stimuli. Many of these do not at present permit a clear cut, convincing analysis.

#### SUMMARY

1. Inhibition of anaphylaxis in lower animals has been induced by the extirpation of the parathyroid, thymus and particularly the thyroid gland.

2. Acceleration of anaphylaxis may be brought about by ovariectomy and hypophysectomy, but most consistently by experimental hyperthyroidism and adrenalectomy in rats.

3. Removal of the thyroid, thymus and parathyroid in man does not influence the allergic state, testifying to the inherent cellular nature of sensitization.

4. This is also evidenced by the demonstration of sensitization in a three day old chick prior to the development of endocrine glands or nerves, in the excised guinea pig uterus and the explanted mononuclear cells *in vitro*, as well as in homologous human skin grafts.

5. The development or suppression of allergic manifestation during specific endocrinal cycles may be attributed to hormonal or autonomic nervous regulations both of which may increase or lower the threshold of cellular response, but not initiate it. The mechanism involved herein is not clear.

6. Cholinergic fibres receiving stimuli from various sources such as the central nervous system and physical agents such as cold or heat, may induce cellular reactions through release of H. substance in the skin stimulating allergic reactions.

7. Therapy in sensitive individuals subject to allergenic as well as cholinergic influences should be of a character capable of neutralizing or eliminating both factors.

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# HEMATOGENOUS TUBERCULOSIS WITH RECURRENT DISSEMINATIONS

## REPORT OF TWO CASES<sup>1</sup>

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Acute generalized miliary tuberculosis has been a well known clinical entity for many years. While more common in infancy this condition is not excessively rare in adult life. What is less generally known is that the tubercle bacillus can, and frequently does, invade the blood stream to produce limited dissemination in the lungs as well as in other organs and tissues; that these disseminations may occur more than once in the same individual and result in subacute and chronic clinical pictures of great variety. When in 1923 we reported a group of cases with hematogenous chronic pulmonary miliary tuberculosis (1) we were able to find few references to the subject in the American literature. In the recent literature, however, the subject of hematogenous tuberculosis has received increasing attention. In a recent paper Rubin (2) reported an interesting group of cases and reviewed the literature on the subject. The following two case reports are of interest because they illustrate some of the clinical features of this condition when recurrent dissemination takes place. Each case will be commented upon and the subject will then be more generally discussed.

### CASE REPORTS

*Case 1. History.* (Adm. 479442): M. C., a 26 year old female secretary was admitted to The Mount Sinai Hospital on September 23, 1941 with marked adenopathy, moderate fever, pain in the right hip and progressive loss of weight and strength over a period of 13 months.

Her past history was essentially negative and irrelevant. She had no familial or contact history of tuberculosis.

Her present illness began about 13 months before admission. At that time, while on vacation in the country, she fell ill with fever to 104°F., malaise and frequent night sweats, for which she was hospitalized. She remained in the hospital for 3 weeks. Her fever gradually subsided with bed rest and her condition improved generally after a blood transfusion. Although the patient had no pulmonary complaints, roentgen-ray examination of the chest disclosed fine infiltrations in the right lower lobe the nature of which was not clear. While in the hospital she developed a skin lesion on the cheeks and bridge of the nose which was diagnosed as Lupus Erythematosus. About 2 months after the onset she developed post-cervical adenopathy. One month later the patient was again hospitalized because of recurrence of fever. Although she still had no pulmonary complaints roentgen-ray examination of the lungs again showed the lesion in the right lower lobe. Biopsy of a cervical gland confirmed the clinical diagnosis of glandular tuberculosis. Since then there has been progressive and marked involvement of the lymph nodes in the neck, axillae and groin. About 9 months before admission she developed pain in the right hip joint. The pain was throbbing in nature, was made worse by motion and frequently disturbed her sleep at night. This pain persisted to the present time varying in severity from time to time but growing

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progressively worse. It made walking impossible and greatly restricted motion in bed. During all these months there was progressive loss of weight and strength; and the fever which had returned persisted with practically no remission. There was no cough, expectoration or any other pulmonary complaints up to the time of admission to The Mount Sinai Hospital.

*Examination:* The patient appeared pale and chronically ill. There was marked involvement of all the lymph nodes in the neck, in both axillae and right groin. The nodes appeared hard, non-tender, irregular. Some of them were matted together. They were easily movable and not adherent to the skin. They filled the axillae and groin and bulged very prominently in the anterior and posterior cervical regions. The liver and spleen were not palpable, and no masses could be felt in the abdomen.

There was marked atrophy of the muscles of the right lower extremity. The right hip joint showed marked restriction of motion. The roentgen-ray examination of the right hip joint showed moderate decalcification of the sacrum and the ilium immediately adjacent



FIG. 1



FIG. 2

FIG. 1. (Case 1). Roentgenogram of the lungs on admission, showing miliary and submiliary infiltrations in both lungs. The tubercles vary considerably in size and are uneven in distribution, indicating multiple seeding.

FIG. 2 (Case 1). Roentgenogram of the lungs nearly two months later, showing increase in the number and size of the tubercles and, in addition, a pleural effusion at the base.

to the joint. The joint outline appeared somewhat irregular. These roentgen findings were interpreted as consistent with the diagnosis of tuberculous arthritis.

The physical signs in the lungs were few and insignificant. However, roentgen-ray examination on September 24, 1941 (fig. 1) showed scattered miliary and submiliary infiltrations throughout the right lung most marked in mid-portion. In the right lower lobe the infiltrations were larger and appeared older. Fewer but similar miliary infiltrations were present in the left upper lobe.

There was no significant abnormality in the cardio-vascular, urogenital or nervous systems.

*Laboratory Data:* Blood: hemoglobin 60 per cent; red blood cells, 3.3 million; white blood cells, 4,900 with a normal differential picture; sedimentation rate, 18 mm. in 12 minutes; Wassermann reaction and blood chemistry, negative. The electrocardiogram was normal. The gastric lavage showed the presence of acid fast bacilli on the last of several examinations. This finding was confirmed by guinea-pig inoculation and by culture. A biopsy of one of the axillary glands showed caseous tuberculosis. An attempt was made to culture the blood for tubercle bacilli but no growth was obtained.

*Course:* The patient remained in the hospital for about 2½ months and was discharged unimproved. Her temperature ranged between 98 and 104.2°F. She continued to lose weight and strength, and her other complaints were not improved. About 3 weeks after admission she developed a non-productive cough. Roentgen-ray examination at that time showed an increase in the size and number of the tubercles in both lung fields. Three weeks later she developed severe pleuritic pain in the left chest and roentgen-ray examination of the lungs on November 10, showed a small left pleural effusion in addition to the previous findings (fig. 2). At this time she coughed up some blood-tinged sputum on one occasion. Although tubercle bacilli could not be found on smear of the sputum, they were found in the gastric contents. The patient continued to run a down-hill course and was transferred to an institution for chronic diseases on December 23; she died one month later.

*Comment:* This is a case of hematogenous tuberculosis in an adult involving to a marked degree numerous lymph nodes in various locations, the right hip joint as well as the lungs and pleura. The disease may have involved other organs and tissues without clinical manifestations at the time. It is of interest that the intrathoracic lymph nodes were not notably enlarged in this case. The mode of development of the pulmonary lesion, as depicted by roentgen-ray examinations, indicates that this is a case of hematogenous tuberculosis with recurrent seeding. Pulmonary symptoms did not appear until about the fifteenth month of the patient's illness. The initial symptomless pulmonary lesion was observed at the onset of her acute illness and, no doubt, represented the result of the first seeding in the lung. Figures 1 and 2 show a disseminated miliary and submiliary tuberculosis unevenly distributed in both lungs in addition to the older lesion in the right lower lobe. The varying size and irregular distribution of the tubercles suggest repeated seedings rather than a single hematogenous dissemination. The pleural process in the left lung may be due to hematogenous involvement of the pleura or may be secondary to the evolution of the tubercle in the underlying lung.

In cases of hematogenous tuberculosis the ultimate fate of the patient is determined by the following factors: 1) persistence or healing of the focus from which the invasion of the blood stream has been derived; 2) the evolution of the existing foci of disease, demonstrable or occult, especially those in the lungs, i.e., whether they tend to heal or to break down and spread. The seriousness of the prognosis in the reported case was due to recent further dissemination of the disease and, particularly, to the development of open pulmonary tuberculosis as shown by the appearance of cough and the finding of tubercle bacilli in the gastric contents.

It should be emphasized however, that the prognosis is not necessarily hopeless even in this type of case. The capacity of hematogenous lesions to heal or indeed to absorb completely has been demonstrated repeatedly. It may occur even when dissemination is widespread, as observed in cases of apparently healed pulmonary miliary tuberculosis as well as in other forms of hematogenous tuberculosis.

*Case 2. History:* (Adm. 328124): L. F., a young woman, aged 22 years, was admitted to The Mount Sinai Hospital on July 12, 1935 in the fourth week of an acute illness characterized by headache of increasing severity, vomiting, severe pains in the neck and back and increasing drowsiness.

This patient first came under observation in February of 1932 with signs and symptoms of acute serous effusion in the left chest apparently of tuberculous etiology. The clinical course was of only moderate severity. The fever was not high and subsided in less than 5 weeks. The effusion was not large and absorbed spontaneously in about 2 months. She had no dyspnea. The chest pain was moderate and the constitutional symptoms were mild. She had no cough throughout the entire course. The convalescence was rapid and uneventful.

There was no family or contact history of tuberculosis or any history of antecedent pulmonary disease. Roentgen-ray examination of the lungs 10 weeks after the onset of the illness (fig. 3) showed miliary and submiliary infiltrations in both lungs, most marked in the upper lobes. There was evidence of perifocal exudative reaction about many of the tubercles. The effusion in the left pleural cavity appeared almost completely absorbed. At that time, and for many months after, a few crepitant rales could be elicited over both upper lobes.



FIG. 3

FIG. 3 (Case 2). Roentgenogram of the lungs (4/18/32) showing miliary and submiliary tubercles in both upper lobes with perifocal exudations about many of the foci. Subsiding pleurisy in the left base is also to be noted.



FIG. 4

FIG. 4 (Case 2). Roentgenogram of the lungs (9/8/33) showing marked resolution and fine fibrosis of the lesions in both lungs.

The patient was admitted to a sanatorium three months after the onset of her illness where she remained for about 6 months. That period of sanatorium care and 9 months more of partial activity at home completed her "cure." In September, 1933, 1½ years after the onset of the pleurisy, the patient appeared entirely well. Roentgen-ray examination of the lungs at that time (fig. 4) showed marked resolution of the tuberculous process in both lungs. Intensification of the pulmonary markings due to a fine interstitial fibrosis and the presence of a number of small fibrotic tubercles were the only residua of the previously existing infiltrations in the lungs. There were no significant abnormal physical signs in the lungs at that time. The patient was regarded as "apparently cured" and was allowed to return to normal activity. She remained entirely well and gainfully employed for 22 months.

Her present illness began 4 weeks before admission to the hospital with "nervousness," fatigability, dull headache and pain over the eyes. She attributed these symptoms to excessive physical and mental strain incidental to preparations for her marriage and disregarded them during the first week. Two weeks before admission the headaches became more frequent and more severe. She also began to experience shooting pains "starting

from the heels and traveling up her legs to the spine, to the back and of the neck and head," especially while walking. At the same time she noted that she had fever up to 100.6°F. by mouth. During the following two weeks the symptoms grew progressively worse and the patient had to be confined to bed. One week before admission she began to vomit after each meal. The vomiting was not definitely projectile. Drowsiness appeared and grew progressively worse. Three days before admission strabismus was noted. The patient became irrational and tried to jump out of bed. At this time she was admitted to the hospital. There were no pulmonary symptoms during this entire period.

*Examination:* On admission the patient appeared acutely ill. She was well developed and well nourished and showed no evidence of recent weight loss. She appeared pale, somewhat cyanotic, stuporous and restless. Her right pupil was larger than the left and both reacted sluggishly to light. The fundi appeared normal. There was paresis of the right sixth and seventh cranial nerves. The mouth was kept tightly shut. The tongue was black and dry. The breathing was irregular and moderately rapid. The lungs showed slightly impaired resonance. The breath sounds were harsh; rhonchi and scattered crepi-



FIG. 5 (Case 2). Roentgenogram of the lungs (6/25/35) showing innumerable closely packed miliary tubercles throughout both lungs resulting from another and recent hematogenous seeding.

tant rales could be heard bilaterally. There was no cough or expectoration. The pulse was rapid but of good quality. The blood pressure was 150 systolic and 90 diastolic. The additional significant neurological findings included marked neck rigidity, bilateral Kernig, bilateral Babinski and confirmatory signs.

A lumbar puncture yielded about 15 cc. of clear, colorless fluid. The initial pressure was 250 mm. of water. There was a good response to jugular pressure with a slow fall.

*Laboratory data:* Cerebrospinal fluid: 142 cells, of which there were 32 per cent polymorphonuclear leucocytes, 64 per cent lymphocytes and 4 per cent monocytes. The stained smear showed scattered acid fast bacilli. Guinea-pig inoculation with the cerebrospinal fluid proved positive for tuberculosis. Chemical examination of the cerebrospinal fluid showed: sugar, 11 mg. per cent; chlorides, 538 mg. per cent; tryptophane reaction, negative. Blood: hemoglobin, 90 per cent; 18,000 white blood cells with 90 per cent polymorphonuclear leucocytes. Blood culture showed no growth. Roentgen-ray examination of the lungs (fig. 5) showed both lungs studded with closely packed miliary tubercles from apex to base.

*Course:* The clinical course in the hospital was characterized by a rapid and marked progression of the symptoms and signs of the disease. The temperature ranged from 101

to 103.5°F. The respirations varied between 26 and 38 per minute and became increasingly more irregular in rhythm and character. The pulse rate ranged from 98 to 140. The stupor deepened into coma. There was marked restlessness and increasing twitching of the muscles. Vomiting was frequent. Difficulty in swallowing became progressively more marked. Incontinence developed and persisted to the end. The patient became insensitive to external stimuli. She gradually sank into deep coma and succumbed 2 days after admission to the hospital. Permission for necropsy was not obtained.

*Comment:* The following interpretation of the sequence of events seems to be justified by the clinical course of the case: The pleural effusion in 1932 was a manifestation of hematogenous tuberculosis. The miliary and submiliary lesions in the upper lobes of both lungs represented the pulmonary phase of that hematogenous dissemination. The symmetrical arrangement of the tubercles in both upper lobes, their miliary and submiliary character, and the absence of pulmonary symptoms are all characteristic of a limited hematogenous pulmonary tuberculosis. The satisfactory clinical course during the ensuing 3 years as well as the marked clearing and apparent healing by fibrosis of the pulmonary lesions further support the diagnosis of hematogenous tuberculosis of a benign variety.

The terminal illness was caused by a recurrent hematogenous dissemination of tubercle bacilli which, on this occasion, resulted in acute pulmonary miliary tuberculosis and tuberculous meningitis. This case thus illustrates the benign and serious forms of hematogenous tuberculosis in the same patient both being the result of recurrent dissemination.

#### DISCUSSION

The invasion of the blood stream by tubercle bacilli may be massive and produce a generalized miliary tuberculosis, which can be fatal in a very short time; or it may be extremely limited and attenuated, producing few or no clinical symptoms. Between these two extremes there are many variants in the extent of the dissemination and the severity of clinical manifestations. The tubercle bacilli may spread from a tuberculous focus to invade the blood stream in a number of ways. A common route is from a caseous lymph node by way of lymphatics, to the thoracic duct, thence to the superior vena cava and right side of the heart and to the lungs. In the lungs they may be filtered out and produce hematogenous pulmonary miliary tuberculosis. Some bacilli may pass through the pulmonary capillaries to the systemic circulation and spread either extensively or to a limited degree to various organs and tissues of the body. Another mode of hematogenous dissemination is via a tuberculous focus rupturing directly into a blood vessel (artery or vein). The resulting invasion may be limited or widespread depending on the size, location and distribution of the blood vessel. Then again the tuberculous process may involve a vessel wall and produce an intimal or subintimal focus from which invasion of the blood stream may take place repeatedly and in varying degrees of severity.

The number and virulence of the invading organisms, the frequency of the invasion, the resistance of the host, and especially the site of the entry are significant factors which will determine the extent of the dissemination, whether

limited or widespread, as well as the clinical course of the disease, whether acute, subacute, chronic or latent.

It is now well established that the invasion of the blood stream by the tubercle bacillus is not an infrequent occurrence. Wilson (3) estimated the incidence of demonstrable tuberculous bacteremia to be 36.4 per cent in patients with generalized miliary tuberculosis, and 4.9 per cent in patients with non-pulmonary tuberculosis. Some observers regard this estimate as too conservative, and suggest that, as the technique of blood culture improves, it may be shown that a transitory bacteremia is a common occurrence in all forms and phases of tuberculosis.

The severe forms of hematogenous tuberculosis, generalized miliary tuberculosis and acute pulmonary miliary tuberculosis, are well known entities. These forms result when massive invasion of the blood stream takes place. The phase of "early generalization" which may follow the establishment of the primary complex is an example of a benign form of hematogenous dissemination. In the vast majority of these cases the bacilleemia is transitory and abortive in nature, and does not result in clinical disease. The chronic and benign forms of diffuse pulmonary miliary tuberculosis are other well recognized varieties (1, 4) which result when the invading organism is of low virulence or the resistance of the host is good.

What is less well known is that hematogenous tuberculosis may be of limited distribution involving only part of an organ or tissue, for instance, a portion of one or both lungs; that the invasion of the blood stream may be repeated many times at longer or shorter intervals; that the resulting pathologic foci may become absorbed, may be dormant, or may become active at any time, producing bizarre clinical pictures. For instance, if a secondary or smaller branch of the pulmonary artery is involved the seeding may be limited to one lobe or one pulmonary segment. Similarly, the extent of the dissemination in any other part of the body will be determined by the size and location of the vascular radicle involved and may be marked or limited.

In both reported cases the first hematogenous dissemination was of the limited variety. In Case 1 this was followed by at least one other dissemination which resulted in more extensive pulmonary miliary tuberculosis. The miliary tubercles proceeded to enlarge and some of them ulcerated into bronchi to produce open pulmonary tuberculosis with its attendant dangers of a bronchogenic spread. In this case death resulted from the toxemia of generalized tuberculosis as well as from progressive pulmonary disease.

In the second case, though the first dissemination was more extensive, the resultant miliary pulmonary tuberculosis was of the benign variety and proceeded to apparent healing by absorption and fibrosis. Obviously not all the foci were healed since a secondary and more massive invasion of the blood stream occurred which resulted in the patient's death. There was at least one focus which went on to caseation and ulceration, finally breaking into the circulation, and causing the fatal dissemination of the disease. This may have consisted of a caseous focus in a lymph node or in one of the hematogenous lesions which had caseated.

As was noted before, hematogenous tuberculosis may produce a great variety of clinical manifestations depending upon the tissue or organ, or any combination of these, which may bear the brunt of the seeding. The two reported cases are of interest because they illustrate some of the clinical features of the condition when recurrent disseminations take place.

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# ACUTE SUPPURATIVE THROMBOPHLEBITIS OF THE SMALLER RENAL VEIN TRIBUTARIES

## REPORT OF TWO CASES

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Despite the frequency of suppurative diseases of the kidney, thrombophlebitis of the renal veins is uncommon. This is of especial interest in view of the high degree of vascularity of the kidney and the intimate association of the excretory apparatus with the blood supply. One need only mention in evidence that over injection of the renal pelvis and calices during retrograde pyelography may demonstrate the so-called pyelovenous backflow as well as excretory visualization of the opposite uninjected kidney.

Suppurative thrombophlebitis of the renal veins is not readily diagnosed clinically because the distinguishing features are not clear cut. Reviews of the literature by Hepler and also by Aschner clearly show that such cases have rarely been recognized either pre-operatively or antemortem. This is to be contrasted with the ease of diagnosis in cases of aseptic thrombosis with the resulting picture of renal infarction. The difficulty in diagnosis arises from the fact that chills, fever, sweats, bacteremia and renal tenderness can occur in acute pyelonephritis and cortical abscess of the kidney without the presence of suppurative phlebitis. Such cases frequently recover without nephrectomy by the simple measures of decapsulation and drainage. On the other hand, it is important to emphasize that unless careful dissections are made of the renal vein, it is possible to overlook an area of suppurative phlebitis. It is for this reason that we wish to present two cases of renal sepsis due to suppurative thrombophlebitis of the smaller renal vein tributaries. In both instances the renal veins were traced to the fourth and fifth divisions and thrombi demonstrated in the tributaries draining the involved portion of renal parenchyma.

One can only repeat what has already been stated by one of the authors in a previous paper. The bacteremia of acute pyelonephritis or of cortical abscess of the kidney without renal vein involvement cannot be distinguished from that of a case with renal vein phlebitis. A presumptive diagnosis can be made and only by a process of exclusion. If the clinical course is unusually severe and fulminating in character, involvement of the renal vein should be suspected. If, after a primary operation for suppurative disease of the kidney, the sepsis is not controlled, vein involvement should be considered. If after a nephrectomy for a cortical abscess or carbuncle of the kidney the sepsis persists, the likelihood of a renal vein thrombosis should be borne in mind.

In the present day of sulfonamide and penicillin therapy, it is important to mention their influence on this disease. While their value in infections is unquestioned, our experiences with the sulfonamide group have been that in frank suppurative processes, their continued use to the exclusion of surgery can mask

the clinical picture and lead the physician into a false sense of security. In several instances, the clinical picture of sepsis reappeared with the cessation of the drug and surgical exploration revealed localized suppuration and abscess.

#### CASE REPORTS

*Case 1. History* (Adm. 409619). D. C., a woman, aged 59 years, was first seen May 12, 1937. About seven weeks previously she developed fever and was treated for bronchopneumonia. This seemed to improve after two to three weeks. During this time she developed a furuncle of the axilla which opened and discharged spontaneously. Despite the improvement in the pneumonic condition, she continued to have a fever ranging between 101° and 102°F. The patient was referred to us for examination because of the left kidney tenderness and fever. There had been some loss of weight.

*Examination.* The patient appeared chronically ill. Abdominal examination failed to disclose any abnormality. There was a mass with bulging of the left flank over which there was marked shock tenderness.

*Laboratory data.* Urinalysis disclosed a faint trace of albumin, no sugar and no abnormal microscopic elements. X-ray examination of the abdomen showed blurring of the left psoas margin. Excretory urography and cystoscopy showed no abnormality.

*Course.* She was admitted to The Mount Sinai Hospital and on May 14, 1937 with a pre-operative diagnosis of perinephritic abscess, operation was performed. A well localized perinephritic abscess was found with a large amount of broken down tissue. Culture of the pus showed staphylococcus aureus A.

The patient made a comparatively smooth recovery with subsidence of the fever to normal and she left the hospital June 3, 1937 with the wound almost healed. The day after she left the hospital her temperature rose to 102°F. She was then re-admitted to the hospital with a second chill and rise in temperature to 106.4°F. A pre-operative diagnosis of acute suppurative thrombophlebitis of the renal vein was made.

*Operation.* Left subcapsular nephrectomy was done. There was no pus evident even on decapsulation of the kidney.

*Pathology.* There was a subcortical abscess about 1 cm. in diameter. Dissection of the renal veins showed a thrombo-phlebitis in a fourth order tributary draining the abscess area.

*Post-operative course.* Blood culture taken prior to operation showed the presence of staphylococcus aureus A. Following operation she developed auricular fibrillation and a psychosis. Blood cultures taken on different occasions were positive for staphylococci. She developed metastatic staphylococcal foci in the right shoulder and right wrist. The right shoulder joint area was drained and subsequently evidences of osteomyelitis of the greater tuberosity and head of the right humerus appeared. The psychosis became more marked and the patient gradually deteriorated and finally ceased August 27, 1937.

*Summary.* Onset of bronchopneumonia and furuncle of axilla. Febrile course followed by tender mass in left flank which was found to be a perinephritic abscess and drained. Infection was due to staphylococcus aureus. Subcapsular nephrectomy and specimen showed small renal abscess with thrombophlebitis of tributary of the renal vein. Persistent sepsis with positive blood cultures and metastatic staphylococcal foci to the right humerus, right wrist and elsewhere. Exitus.

*Case 2. History* (Adm. 488930). R. C., a woman, aged 65 years, was first seen by Dr. William M. Hitzig on April 24, 1942 because of a chill. In view of the presence of pus and red blood cells in the urine and also left lumbar tenderness, he made a diagnosis of left calculus pyelonephritis. Thirty-five years previously she passed a ureteral calculus. The

initial chill and fever was followed by another 12 hours later. Then they recurred at 12 to 15 hour intervals. During these 48 hours she received 12 grams of sulfadiazine without any influence upon the chills and fever. The patient was therefore admitted to The Mount Sinai Hospital on April 26, 1942.

*Examination.* The patient was an acutely ill woman. The only abnormality on examination was the presence of slight left lumbar tenderness.

*Laboratory data.* Blood urea nitrogen was 16 mg. per cent. Urine examinations on 3 successive occasions failed to show pus. Flat x-ray examination of the genito-urinary tract revealed an irregular calculus in the lower calyx of the left kidney. Excretory urography disclosed a normal right kidney. The left kidney was likewise normal except for a dilated lower calyx in which the calculus was present. Cystoscopy revealed the bladder and ureter orifices to be normal. The excretion of indigo-carmin from both kidneys was equally good. A blood culture which was taken on admission showed the presence of *B. coli* with innumerable colonies per cubic centimeter of blood. Culture of the urine from the left kidney also showed *B. coli*. In view of these findings, operation was carried out April 27, 1943.

*Operation.* The left kidney was normal except for some adherent perinephritis over the lower pole. After resecting the eleventh and twelfth ribs, the left kidney was removed by ligation and cutting the renal pedicle and ureter.

*Pathology.* The kidney showed acute and chronic pyelonephritis with abscess formation and thrombophlebitis of small branches of the renal vein.

*Course.* Patient made a comparatively uneventful convalescence except for a wound infection. She was discharged from the hospital June 1, 1942 and has remained well since.

*Summary.* Typical picture of renal sepsis, with chills, fever to 105°F., left kidney tenderness, positive blood culture. Preoperative examination showed a calculus in the lower calyx with excellent function of the left kidney. Nephrectomy was done with complete recovery. The kidney specimen showed acute and chronic pyelonephritis with thrombophlebitis of a tributary of the renal vein.

#### CONCLUSIONS

1. Two cases of sepsis due to thrombophlebitis of the smaller tributaries of the renal veins were presented.
2. The differential diagnosis between suppurative infections of the kidney and those associated with suppurative thrombophlebitis is very difficult.
3. The treatment of the latter condition is best carried out by nephrectomy.
4. Although suppurative thrombophlebitis of the renal vein is uncommon and the pre-operative diagnosis is presumptive, unless careful dissections of the renal vein tributaries are carried out, the lesion may be readily overlooked.

## BRONCHO-PULMONARY MONILIASIS

### CASE REPORT WITH PATHOLOGICAL STUDY

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Because of the rarity of necropsy reports in monilia infections of the lung, the following case with complete autopsy findings is deemed worthy of record.

The diagnosis in this case may be questioned because the monilia were not recovered bronchoscopically nor identified in sections of the tissues obtained at post-mortem examination. However, over a period of two years they were a constant finding in the sputum and were confirmed by cultures and animal inoculations.

As will be noted from the post-mortem findings, the pulmonary changes were identical with those of broncho-pulmonary moniliasis encountered clinically and experimentally. Moreover, the absence of monilia in the tissues may be no greater objection to the diagnosis in this condition than that of spirochetes in pulmonary syphilis. One advantage in the latter, however, is the presence of gummata at times in other organs such as the liver and spleen. Certain inclusion bodies associated with giant cells are suggestive in this case, particularly in connection with similar findings in the kidney.

The following is quoted from an article by Kino. "A systemic dissemination of the pathogenic monilia appears as a possibility as shown by the recovery of the organism from the urine in cases of bronchopulmonary moniliasis. No other definite etiologic agents were demonstrated in the pulmonary lesions at necropsy.

"This may in part be due to the fact that the hematoxylin-eosin stain does not bring them out.

"The question of whether broncho-moniliasis constitutes a primary disease entity cannot readily be answered. Certainly the clinical diagnosis of this condition through the mere demonstration of pathogenic monilia in the sputum seems unjustified. Evidence at hand appears to indicate that monilia is probably a secondary invader in a primary lesion already in existence and that it contributes largely to the continued and progressive activity of that lesion. There are, however, several pertinent observations which may be advanced in favor of the opinion that the fungus may, in a limited sense at least, act as an etiologic agent: 1) the therapeutic effect of iodides; a marked symptomatic improvement, and often complete clinical cure have been reported; 2) a likely systemic dissemination of pathogenic monilia as evidenced by the recovery of this organism from the urine in cases of broncho-moniliasis and by the demonstration of the yeast-like bodies in the regional lymph nodes and in the spleen; 3) no other definite etiologic agents are demonstrated in the pulmonary lesions at necropsy; 4) the condition is undoubtedly consistently overlooked in routine

necropsies, due chiefly to the failure to carry out certain technical details for the demonstration of the organism in culture as well as in the lesion; 5) human lesions can be reproduced in laboratory animals in which the organism is highly pathogenic; 6) finally, allergy appears to play an important role in the pathogenesis of this condition as suggested by the experiment of Kurotchkin and Lim.

"The sequence of events leading up to the development of this condition may be described as follows: The fungus gains its entrance in the lower air passages and begins to multiply in the inflammatory exudate in the presence of bronchitis, bronchiectasis or pneumonia. It may penetrate the wall of the bronchus or reaching the alveoli, invade the pneumonia area, to prevent resolution and to continue to multiply, producing a low-grade suppurative inflammation. This may continue indefinitely, perhaps for many years, predisposing the affected individual to periodic attacks of pneumonia which sooner or later result in a chronic lesion with areas of fibrosis and suppuration. It would thus appear that a pre-existing, primary lesion in the lung is essential to initiate the infestation by the fungus.

"Certain mycotic infections of the lungs have long been recognized as entities. Blastomycosis and actinomycosis are the common examples. Their known pathogenicity in man and their ability to readily produce local lesions, to cause a systemic invasion, visceral involvement and eventual death have established them as definite clinico-pathologic entities. Monilia, on the other hand, is comparatively less pathogenic to man and often leads a tenacious, saprophytic existence in human tissue. However, given a primary lesion in the lung with probable attendant biochemical tissue changes affording a favorable medium for its unrestrained growth, coupled with the inherent or acquired susceptibility of the host, the fungus may become distinctly pathogenic in the lung of the affected individual and produce a chronic suppurative inflammation known clinically as broncho-moniliasis."

The disease was first described by Castellania in Ceylon in 1905. Since then cases have been reported from all countries except Australasia. It is apparently more common in tropical and subtropical countries and its occurrence is probably more frequent than recognized. "Although parasitic in many human mouths, when found in large numbers broncho-moniliasis is usually indicated." It is prone to develop after a primary irritating factor, bacterial, toxic, or mechanical. In the case reported herein trauma may have been an exciting factor (Warr). It was also observed in this case that the fungus disappeared after intensive treatment with potassium iodide.

In common with many reported cases the lesion seems to have started at the base of the lung and its initial appearance at the base of the left lung may be of some significance. This is a frequent location for aspiration infections of other kinds. Although frequently found as a saprophyte in tuberculosis and in carcinoma, it is believed by some observers that the fungus infection may precede the tuberculous. The absence of all mouth lesions in this case may also be in favor of a primary lung infection.

## CASE REPORT

*History:* The patient was a white, adult, single female nurse, 61 years of age. Her family history was negative for tuberculosis; her mother died of cancer of the uterus; her father died of cardiac disease. She had mumps and chicken pox in childhood. For 19 years she had been working as a nurse in a tuberculosis clinic. During this time she had frequent routine chest films which, up to her present illness, revealed nothing abnormal.<sup>1</sup> In 1927 she had a small cyst removed from each breast. In 1938 she was treated for some allergic condition of the skin and conjunctiva. She passed through her menopause at the age of 51 years.

Her present illness seemed to date back to October, 1939, when she developed a fairly persistent, dull, aching pain in the lower left axillary region of her chest. This was attributed to the after effects of an automobile accident. She continued to work until November, 1939, when she suddenly experienced a sense of constriction in her chest that was relieved by standing still for several minutes. She developed a productive cough, and was then put to bed for several days but was able subsequently to return to work. One week later pain in the chest returned; this time it was attributed to pleurisy. She was again put to bed. In December, 1939, she was admitted to Christ Hospital where an x-ray examination of her chest revealed the presence of fractured ribs. The lung fields were apparently normal. An electrocardiogram was also negative.

She was first seen by me on January 9, 1940. She complained of pain in the left lower chest, in the upper dorsal region of the back, dyspnea in the morning and on effort, and a dry morning cough. She had by this time lost about 25 pounds.

*Examination:* The patient was a very poorly nourished, elderly woman, who was rather hyposensitive. Her eyes were negative except for early arteriosclerotic changes in the retinal vessels. The mouth was negative except for partial dentures, and retraction of the gums about the few remaining teeth. There was tenderness along the left costal arch with some nodulation of the ninth rib. The lungs were negative. The heart borders were rather obscured but there was no heaving. The heart sounds were fairly clear and of good quality. The abdomen was tympanic. On fluoroscopic examination of the chest the lungs were found to be apparently clear; there was a slight left ventricular enlargement, a redundant and sclerotic aorta with prominence of the ascending portion of the arch.

*Laboratory Data:* Electrocardiogram revealed depression of the ST segments in lead II and very large P waves, as well as diphaseic T waves in the precordial lead CF IV. These changes were even more pronounced one month later when the T waves in leads I and III were almost iso-electric, while definitely depressed in lead II. Three months later there was considerable improvement in the first two leads, although there was still slight depression of the RT segments. Following an exercise tolerance test on May 6, 1940, there appeared to be no changes to suggest coronary insufficiency. The general pattern of the cardiogram persisted and was still noticeable on January 23, 1941, at which time the T waves in leads I and II were normal but iso-electric in lead III, while the ST segments in CF IV were elevated.

The blood pressure when she was first seen was 140 systolic and 88 diastolic. The pulse rate ranged from 85 to 100 per minute. Subsequent blood pressure readings were always lower, ranging between 96 to 126 systolic and 70 to 80 diastolic.

An x-ray examination of the chest, January 9, 1940, revealed increased pulmonary markings throughout and particularly at the left base. The heart was normal in contour and apparently within normal limits, although the apex was obscured by the combined shadows of the breast and mottling at the left base. There was also some fullness of the conus. The aortic knob looked normal except for a small plaque of calcium.

A study of films made at Christ Hospital on December 19, 1939 (fig. 3) revealed an incomplete fracture of the ninth rib on the left side. Evidence of this with callous formation was

<sup>1</sup> A routine chest film in 1937 (fig. 1) revealed no abnormal findings. However, mottling was elicited at the left base on January 26, 1939 (fig. 2).

still visible April 4, 1940 (fig. 4). At this time more mottling appeared at the bases with some increase in the markings throughout.

*Course:* The patient was slowly losing weight. On March 5, 1940, basal metabolic studies revealed a normal rate. Her temperature was normal. From time to time she had attacks of dyspnea lasting half an hour without pain, occasionally awakening her at night.



FIG. 1

FIG. 1. March 19, 1937. Film taken during routine annual x-ray check-up. Lung findings were essentially negative.

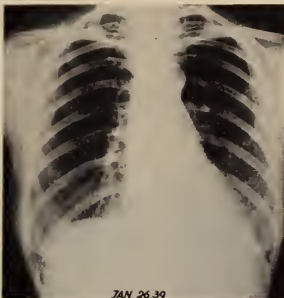


FIG. 2

FIG. 2. January 26, 1939. This was also a routine check-up film. Note slight mottling at left base, the significance of which was not appreciated at that time.

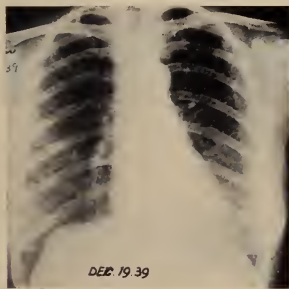


FIG. 3

FIG. 3. December 19, 1939. Film taken following automobile collision. Note fracture of ninth rib on the left side.

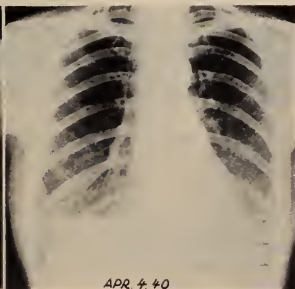


FIG. 4

FIG. 4. April 4, 1940. Note mottling at both bases, particularly at left and callous formation at the site of previous fractures involving the eighth and ninth ribs on the left side.

At one time she complained of painful swelling of her fingers. She was unable to lie on her left side or take a deep breath without discomfort. Her sedimentation time was normal, and the circulation time was only 15 seconds (arm to tongue). It was evident that her dyspnea was not cardiac in origin, but rather pulmonary.

In June, 1940, she began to have definite episodes of smothering occurring in the morning.

She was often relieved by sitting up for 15 minutes after awakening. She was unable to walk a block and required three pillows to sleep on. Her general condition by this time was poor; she was wasted and pale. There was still no evidence of hyperthyroidism. The x-ray examination showed increased mottling throughout both lungs, which became more pronounced during the following month (fig. 5).

On July 22, 1940, when she was admitted to the Hudson County Tuberculosis Hospital, her dyspnea was so marked that she required oxygen.

The clinical picture at first suggested the possibility of arteriosclerotic heart disease with myocardial damage complicated by some type of involvement of the rib, which was either traumatic or possibly neoplastic. The significance of the mottling at the left base was not fully appreciated at this time. The possibility of malignancy with miliary metastases to the lungs was also considered, but careful study of the gastro-intestinal tract failed to reveal evidence of a primary lesion there.

She remained at the hospital only ten days. During this brief stay her sedimentation time was found to be rapid in spite of a normal temperature. She had a slight leucocytosis,

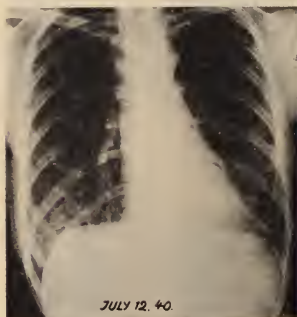


FIG. 5

FIG. 5. July 12, 1940. Note further extension of mottling, some of which has become confluent.



FIG. 6

FIG. 6. May 26, 1941. Note further confluence of densities. Patient now hospitalized

12,650. The Wassermann reaction was negative. The x-ray films of her chest showed much more mottling throughout both lungs, now more patchy in character. Repeated examinations of her sputum for tubercle bacilli were negative.

At home she suffered so much dyspnea on effort that she was bedridden and had to resort to oxygen.

In spite of the fact that her symptoms seemed to be due to myocardial insufficiency, cardiotherapy was to no avail. The suspicion of carcinoma was further strengthened at this time by the discovery of a discrete movable nodule in the outer half of the left breast. However, biopsy proved it to be a benign cystic lesion.

In December, 1940, clubbing of her fingers was noted. The persistent absence of tubercle bacilli in her sputum, the peculiar diffuse mottling in the lungs, and the white cotton-like sputum that was very abundant, although odorless, raised the suspicion of a fungus infection. She was, therefore, put on iodides and seemed to respond favorably until she developed a gastric disturbance. It was then learned that in February, 1938, she had been treated for an unusual conjunctival infection, the cause of which was suspected to be a fungus. She was then put back on iodides gradually increasing the dose from 10 to 30 drops

three times a day. The sputum became more liquid, and easier to raise; she became less dyspneic. She was even able to be up and about a little. She noticed that the sputum, although plentiful, was sticky, tenacious and bubbly.

Meanwhile, x-ray examinations of the chest revealed a gradual increase in the degree of mottling, much of which was now confluent in scattered, coarse patches (fig. 6). In September, 1941, her condition became so poor that she had to be re-admitted to the hospital. She was running a low-grade fever, never higher than 101°F., which subsequently became normal. X-ray examination of the chest then revealed diffuse involvement of both lungs (fig. 7). The sedimentation time was persistently rapid. The sputum was mucoid and negative for tubercle bacilli.

She gradually developed a mild anemia; hemoglobin, 76 per cent; red blood cells, 4,000,-000. There was nothing significant in the differential white blood cell count. The urine was persistently negative except for leucocytes and occasional red blood cells. The blood chemistry findings were within normal limits.



FIG. 7

FIG. 7. September 11, 1941. Note diffuse involvement of both lungs



FIG. 8

FIG. 8. January 10, 1942. Portable film showing further extension with confluence of lesions.

Shortly after her re-admission and on numerous subsequent occasions cultures of the sputum revealed *monilia albicans*. Animal (rabbit) inoculations at this time with cultures of the *monilia* produced fatal pulmonary edema on intravenous injection. Intratracheal injection produced subacute pneumonia and revealed the presence of *monilia* in the alveolar macrophages. No proliferative changes were observed as the animal died in eight days. Intravenous injection when repeated in a male rabbit, again caused death from pneumonia in twenty-four hours. No renal infarction was found. Another rabbit, female, injected intratracheally, died one week later. Sections of the lungs revealed subacute pneumonia with *monilia* in the alveolar macrophages.

The patient's sputum continued to show *monilia* until January, 1942, when, as a result of large doses of iodides, they disappeared. Intradermal injection with 0.1 cc. of a *monilia* vaccine obtained from Dr. Martin of Duke University revealed a definite sensitivity. One-half hour after the injection, a wheal 1 cm. in diameter developed with an erythema 1.9 cm. This gradually increased so that at the end of one and a half hours the wheal was 2.1 cm. and erythema had reached 2.5 cm. The erythema gradually disappeared, but at the end of two and one-half hours the wheal persisted. Attempts were then made to desensitize

her with this vaccine. She continued to do poorly, developing more frequent attacks of paroxysmal dyspnea in spite of increasing doses of iodides and had to receive oxygen constantly. The left lung was filled with musical râles, and there were diminished breath sounds over both lower lobes. Retraction of the intercostal spaces was very noticeable during inspiration. At the suggestion of Dr. Martin of Duke University, intravenous injections of 1 per cent gentian-violet were attempted, but because they were not well tolerated, were discontinued. The patient was obviously suffering from an increasing pulmonary fibrosis (fig. 8) and declined rapidly, losing weight appreciably due to lack of appetite. Although her dyspnea was severe, there was no cyanosis and she seemed to get considerable relief from as little as two liters of oxygen per minute. Her sputum remained clear, glary and tenacious. Any attempt to reduce it with atropine made matters worse because of the inability to expectorate. Despite her emaciation and dyspnea, her peripheral circulation and heart action, as well as her color, remained good. She seemed to get relief in her paroxysms of dyspnea by raising her left arm. Her distress became so marked that despite her dyspnea, she had to be relieved by small doses of morphine. Even when this was increased, it seemed to have no depressing effect on her respiration. Finally she had to get  $\frac{1}{4}$  gr. doses of morphine about every three hours to relieve the distress of her dyspnea. On December 20, 1942, her pulse became weak and irregular, her general condition became grave, and three days later she expired.

During the latter part of her illness the course was characterized by constant dyspnea with frequent paroxysmal exacerbations, anorexia, extreme emaciation and weakness, cough with choking spells, caused by sputum that was sticky, frothy, and white, tightening pains in the left chest and troublesome abdominal distention complained of as "gas."

*Necropsy findings: Abdomen:* The panniculus is very thin and the subcutaneous fat tissue is atrophied. There is marked atrophy of the pre-peritoneal fat and of the mesenteric fat tissue. The vessels in the mesentery and posterior peritoneum stand out distinctly. The omental fat is also atrophied. The *situs viscerum* is normal. The liver and spleen are well hidden under their respective costal margins. The peritoneum is smooth and glistening. There is no free peritoneal fluid.

*Chest:* The right lung is fused on all aspects to the chest wall and diaphragm. The left lung is free and its pleura smooth and glistening. Upon elevating the sternum the mediastinal fat tissue overlying the heart is seen to be atrophic and filled with gas bubbles. These extend from the sternal notch to the xyphoid process. Upon dissecting away the anterior mediastinal fat tissue air bubbles are also found in the external pericardial tissues. There is also some emphysema of the medial aspects of the mediastinum where the lung is adherent to the pericardium (right lung). The right lung is removed from the chest with some difficulty. There is no emphysema of the structures of the neck. The lungs together weigh 720 Gm. They are small just as all the other organs are.

The right lung shows thickening of the visceral pleura. The adhesions have been described. Projecting from the surface of the right lung, particularly over the lower lobe there are numerous emphysematous blebs varying in size from 1-2 cm. in diameter. The lungs, however, are not crepitant except over these emphysematous areas. On the whole the lungs impart a feeling of being fleshy. The illusion of crepitation is given by the emphysematous blebs. On section there are seen scattered such emphysematous blebs particularly in the lower lobe. The cut surface of the lung shows a somewhat accentuated alveolar structure with alternating zones which are of a slate grey color in which the alveolar architecture is not distinct at all. Such areas are irregular in shape and size and sometimes occupy about  $\frac{1}{2}$  or less of a pulmonary lobule. These areas on the whole are seen to be located principally subpleurally. At the apex there is one such dense airless segment measuring approximately 2 cm. wide and 4 cm. long. A larger one is present in the lower lobe posteriorly occupying approximately  $\frac{1}{2}$  of the inferior posterior segment. With such slate grey firm areas there are some emphysematous blebs. The middle lobe also contains many such fibrosed airless portions.

The left lung similarly on its surface presents many emphysematous blebs principally in

the lower lobe and of an appearance similar to that described in the right lung. Here also there are present scattered firm slate grey fibrous areas in the apex and along the postero-lateral portions of the upper and lower lobes and these areas similarly contain emphysematous blebs. The adjacent pulmonary tissue which can be differentiated from such slate grey areas shows either normal or accentuated alveolar architecture. The distribution of these slate grey fibrosed areas is rather irregular, although in the main both lower lobes are more strikingly involved. The pleura overlying the left lung as on the right side is somewhat thick and opaque. Aside from these firm fibrosed areas there is nothing exceptional within either lung. There are no areas of breakdown and nothing distinctive. The trachea shows marked atrophy of muscles and the tracheal cartilages stand out distinctly. The main and branch bronchi grossly appear normal. The bronchi to the lower lobe contain a small amount of very thick viscid mucous exudates. The mucosa appears pale and smooth. The tracheo-bronchial lymph nodes are small and moderately anthracotic. The pulmonary vessels are somewhat thickened and show scattered atheromatous plaques along their entire course.

*Heart:* Weight, 150 Gm. The pericardium contains about 25 cc. of clear amber fluid. The pericardium is smooth and glistening. There is atrophy of the epicardial fat tissue. The myocardium is flabby and brown. There is slight right ventricular hypertrophy and dilatation. The left ventricle is normal in size. The valves and endocardium aside from some opacity show nothing unusual. The coronary ostia and lumina are patent. The aorta shows a minimal degree of atheromatous deposits along its course. These are more prominent in the lower abdominal portion.

*Liver:* Weight, 520 Gm. The capsule is smooth and glistening. The parenchyma is of a deep brown color. On section the lobules are seen to be small but the lobular architecture is distinct. The hepatic and portal vessels are normal. The gall bladder and bile ducts are normal.

*Spleen:* Weight, 40 Gm., smaller than normal in size. The capsule is smooth. On section it is moderately firm. The trabeculae and vessels stand out prominently. The malpighian follicles are not distinct. The pulp does not scrape. The splenic vessels are normal.

*Adrenals:* Small, displaying on section distinct cortico-medullary differentiation.

*Pancreas:* The lobular architecture is evident. The organ is brown in color.

*Genito-Urinary Tract:* The kidneys are small, normal and equal in size. They weigh together 120 Gm. The capsules strip readily revealing a relatively smooth surface with only an occasional small pitted depression. On section the kidneys are brownish-red. The cortico-medullary differentiation is distinct. The glomeruli stand out as pin-point reddish dots. The calyces, pelves, ureters and bladder are normal. There is nothing noteworthy in the genital tract.

*Gastro-Intestinal Tract:* The esophagus, stomach, small and large intestines do not show anything of significance, except for a pea-sized pedunculated polyp in the sigmoid.

*Lymph Nodes:* There is no significant lymph adenopathy.

*Thyroid:* The thyroid is small, firm and very fleshy.

#### MICROSCOPIC OBSERVATIONS

*Heart:* Left ventricle—A section of the left ventricular wall shows small muscle fibers with deposits of paranuclear brown pigment granules. There are no other alterations.

Right ventricle—A section of right ventricular wall shows a similar appearance except for very small foci of muscle cell hypertrophy and very occasional round cell interstitial collections.

*Lungs:* A number of sections of lung are taken for histologic study. These present a more or less similar picture in varying degrees (figs. 9-13). Uniformly

there are extensive areas of organization of the pulmonary tissue with scattered pseudo-glandular structures, markedly dilated bronchioles and bronchi (fig. 9). Throughout the organized areas there is a diffuse round cell and plasma cell infiltration. Often isolated markedly dilated single or groups of alveoli are present either within or adjacent to these organized areas. Throughout, in such areas of organization, there are many foreign body giant cells. Only an occasional one seems to contain a hollow space reminiscent of a dissolved foreign body. In addition there are foci, very small, in which some of the alveoli contain

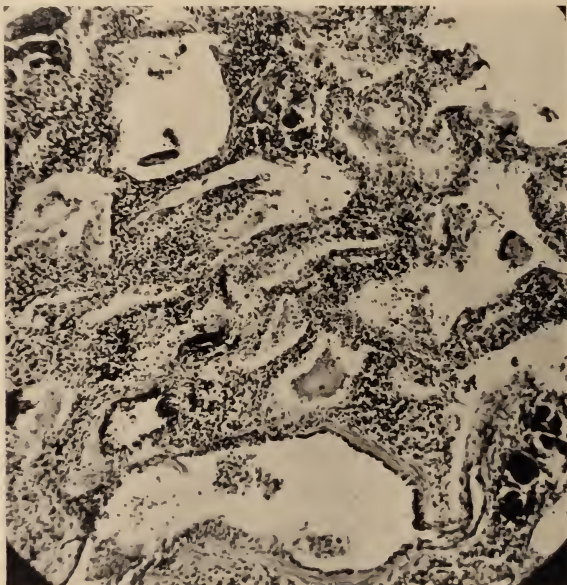


FIG. 9. Low power view showing extensive fibrosis, dilated bronchioles, and severe inflammation of the lung.

collections of polymorphonuclear cells admixed with desquamated alveolar epithelial cells and round cells. Likewise, there are other foci in which the alveolar lumina are filled with an exudate of desquamated cells and monocytes. These are often surrounded by a pink staining pale fluid reminiscent of amucinous material. These often show foreign body giant cells. Scattered throughout all sections there are peculiar collections, sharply circumscribed, of deep blue staining bodies (figs. 10 and 11). These peculiar bodies vary in shape and size. They are sometimes round, other times elliptical or oblong. They are stained

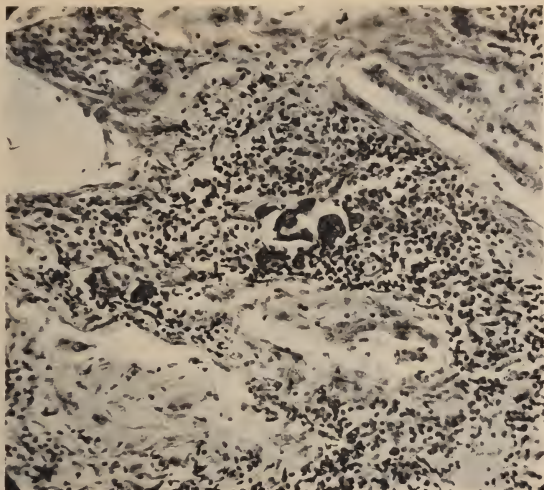


FIG. 10. Medium power view showing organizing inflammation of the lung with deep staining bodies in the septa.

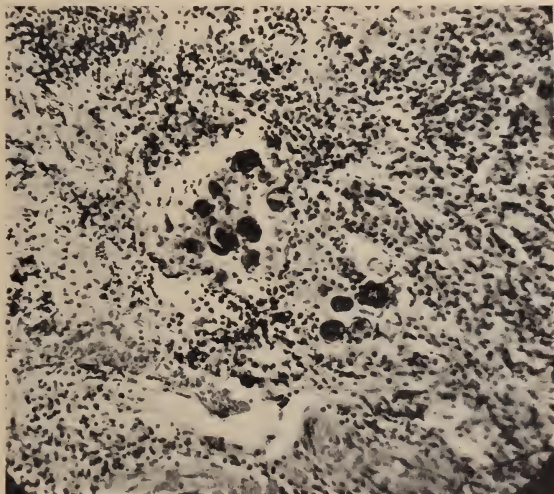


FIG. 11. Medium power view of the lung showing groups of deeply stained bodies surrounded by extensive inflammation.

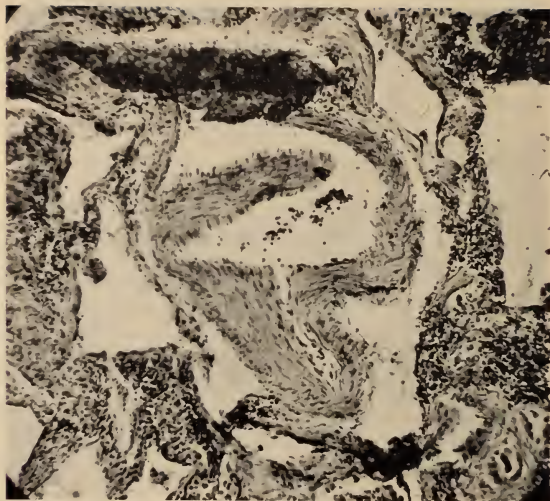


FIG. 12. Extensive interstitial inflammation with dilated alveoli

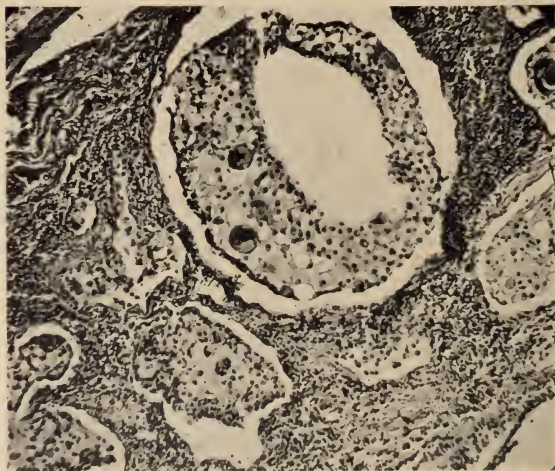


FIG. 13. Medium power view showing alveolar exudate composed of monocytes with alveolar epithelial giant cells.

very deep blue and no characteristic structure can be made out. Sometimes they present a somewhat lamellated appearance and other times they appear amorphous. They are present in groups but of varying size, principally located in the denser portion of the connective tissue. Almost all of them are surrounded by a narrow layer of connective tissue with surrounding large histiocytic cells. Most of these bodies contain simple clear spaces and it is difficult to determine whether they are thus formed or whether anything has been washed out. Sometimes some of these bodies are solid in which case they are deeply stained and as mentioned either amorphous in appearance or suggest lamellation. Individual bodies are 4 to 5 times the size of a lymphocyte. Rarely are they specifically circular, most often being irregular in shape. With the Gram stain they are moderately blue. They do not stain for *calcium* although on hematoxylin stain they suggest calcified bodies like so-called psammoma bodies. Occasional thick coarse deep blue strands are present. Their peculiar shape, appearance and distribution are unlike that of any known fungus or other foreign substance. All of them are deeply imbedded in the organized pulmonary tissue. Some are surrounded by large foreign body giant cells, others by macrophages or large histiocytes. Occasional groups of such bodies are located about bronchi, others in alveolar septa which are markedly thickened and still others near the pleural surface in dense connective tissue. None are found free in the alveolar lumina. They bear no relation to blood vessels or lymphatics apparently. They are not present in areas of acute exudate. Occasionally such bodies consist of a paler rim of light blue stained clearer material containing a large darker central deep blue staining nuclear-like substance. Such an appearance, however, is not common. Occasionally they form large groups occupying approximately a high power field. In such larger groups the lamellated appearance is more evident. Here they appear to resemble some peculiar type of crystal. Throughout all lung sections there is pronounced dilatation of the alveoli in the uninvolved section. The predominant picture, however, is that of marked thickening of the alveolar septa adjacent to areas of organization and pronounced widening of the bronchi with inflammatory cell infiltration of the bronchial walls (figs. 12 and 13). There are focal areas of alveolar congestion. There are no significant vascular changes evident. With the Gram stain no other fungal or bacterial structures are found.

Iron stain shows slight iron content of the bodies. The remainder of the lung has no iron.

The Van Gieson elastica stain shows extensive elastification of the fibrosed lung tissue. The arteries and arterioles throughout show extensive intimal proliferation with moderate to marked narrowing of the lumina and elastica reduplication. The bodies do not contain elastic fibres.

*Tracheo-bronchial lymph nodes:* Several lymph nodes show a similar picture. There is a moderate degree of anthracotic pigment deposition. The lymphatic sinuses are wide, many are filled with pink staining fluid and others contain blood. The lymphatic follicles do not show germinal centers. The laryngeal sinuses are dilated and likewise filled with pink staining fluid. Occasional pigment con-

taining macrophages are seen. The histologic picture is totally insignificant and apparently bears no relation to the process in the lungs.

*Liver:* In areas the liver cells contain a good deal of brown granular pigment. There is some sinus congestion. The portal fields show a very minimal round cell infiltration. The liver cells on the whole seem well preserved.

*Spleen:* The splenic follicles are prominent. There is a good deal of cellularity of the pulp. The sinuses are dilated and somewhat congested.

*Pancreas:* No significant histologic alterations.

*Adrenals:* No significant histologic alterations.

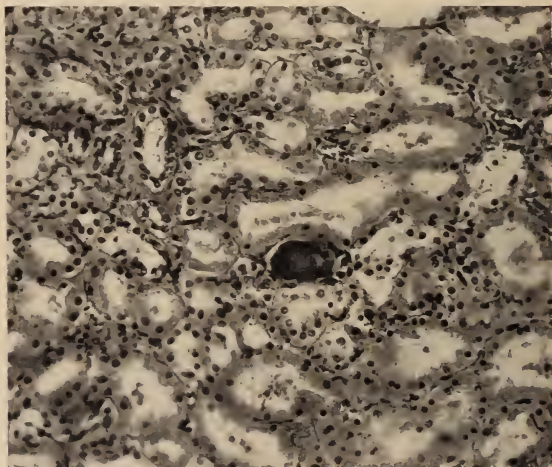


FIG. 14. Medium power view of the kidney showing deeply stained body in the interstitial tissue.

*Kidneys:* There are very small foci of increased interstitial tissue with atrophy of the adjoining tubules. The glomeruli appear essentially normal. There is some degeneration of the glomerular and tubular epithelium. The blood vessels appear normal. Within the kidney (fig. 14) there are seen deep blue staining somewhat circular bodies resembling those seen in the lung. They are located in the interstitial tissue between the tubules and seem to be composed of an amorphous uniform material with interstitial spaces as if some substance had been dissolved out. The mass resembles a crystalline material. Adjacent there is a large giant cell.

*Ovary:* There is atrophy of the ovary.

*Uterus:* There is atrophy of the endometrium. The myometrium appears normal.

*Mediastinal Fat Tissues:* Aside from spread of the fat tissue by air spaces (mediastinal emphysema) there is nothing noteworthy.

*Fallopian Tube:* There are several large serous cysts, thin walled, containing amorphous pink material. The tubal mucosa is intact.

*Thyroid:* The gland on the whole appears essentially normal except for some prominence of the smaller follicles suggesting possible regression of the gland.

*Stomach:* No significant histologic alterations.

*Colon:* There is a large polyp containing typical intestinal glands with elongated closely packed cells containing deep staining nuclei. There is no invasion and no significant atypical features.

#### COMMENT

The symptoms, clinical and laboratory findings in this case were those of a grave type of monilia infection of the respiratory system. The pathogenicity of the fungus was confirmed by cultures and animal inoculation. The clinical and post-mortem findings were not associated with, nor apparently due to, any other recognized etiologic factors such as tuberculosis, carcinoma, syphilis, silicosis, and so forth.

The autopsy findings were those of extreme pulmonary fibrosis with secondary bronchial changes such as those found in cases of broncho-pulmonary moniliasis. The absence of recognizable fungi does not necessarily disprove their etiologic role any more than does the absence of spirochetes in late syphilitic lesions.

The presence of "peculiar collections of sharply circumscribed deep blue staining bodies" is significant particularly in view of the same findings in the kidney sections and may be characteristic of late changes.

#### SUMMARY

A case of chronic broncho-pulmonary disease is reported. It terminated in pulmonary fibrosis in which no other cause could be discovered clinically or at post-mortem examination, except the constant presence of monilia albicans in the sputum and peculiar bodies in the lung and kidney sections post-mortem.

The monilia, although obtained from the oral cavity, were not associated with any visible lesions in the mouth, were recovered in cultures and proved pathogenic for rabbits, in which they produced pulmonary changes associated with monilia in the alveolar macrophages after intratracheal injection. Intravenous injection was promptly lethal. It would therefore seem reasonable to assume that the monilia found in this case were the causative agents.

Intensive iodide therapy gave but temporary relief although followed by a disappearance of the fungus.

The pulmonary fibrosis may have been intensified by the iodides.

There was no response to monilia vaccine and gentian-violet intravenously was not tolerated.

The author is indebted to Dr. B. S. Pollak, Director of the Hudson County Tuberculosis Hospital, Dr. Alfred Kruger former resident physician for their cooperation in the care of the patient and also to Dr. I. E. Gerber, pathologist, for his valuable aid in the laboratory and post-mortem studies.

Grateful acknowledgment is also due Drs. Donald S. Martin and Roger D. Baker of Duke University School of Medicine for many valuable suggestions.

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# POSITIVE PREGNANCY TEST WITHOUT ENDOMETRIAL DECIDUA; ECTOPIC PREGNANCY<sup>1</sup>

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The diagnosis of an unruptured ectopic gestation remains a difficult one. With a typical clinical history and positive pelvic findings with or without a positive pregnancy test, the diagnosis is evident. In the two cases to be reported neither the history nor the gynecological findings were typical. No decidual reaction was found in the endometrium. The indication for laparotomy became definite with the persistence of a positive pregnancy test.

The value of curettage in differentiating between an intrauterine and extra-uterine gravidity has been stressed by many authors. The finding of a decidual

TABLE I  
*Seven series of ectopic pregnancies with endometrial studies*

AUTHOR	REF. NO.	TOTAL CASES	DECIDUA PRESENT	PERCENTAGE
Sampson.....	10	25	5	20
Geist and Matus.....	3	39	23	58.9
Moritz and Douglas.....	4	53	8	15.1
Boerner.....	5	30	14	46.6
Siddall and Jarvis.....	6, 7	38	23	60.5
Goldblatt and Schwartz.....	8	32	14	43.7
Novak.....	9	21	10	47.5
		238	97	40.7

endometrium in the absence of chorionic villi is suggested as strong evidence for the presence of an ectopic pregnancy. Cases such as reported by Frank (2) where the patient passed a decidual cast followed in 24 hours by a degenerated ovum are quite rare. Occasionally the reverse has been seen, that is the early death with expulsion of a young ovum so that on curettage only decidual reaction of the endometrium is found. Under these circumstances, the pregnancy test becomes negative soon after curettage.

A review of the literature reveals that, for the most part, the finding of decidua in the uterine endometrium of patients with ectopic pregnancy decreases when the patient has bled profusely or for a long period of time. An exception to this statement may be noted in six cases of the series reported by Moritz and Douglas (4). Despite the absence of bleeding they found no decidual reaction in the endometrium. The tubal chorionic villi in these patients were reported as intact in three, degenerated and intact in three.

In seven series of ectopic pregnancies (Table I) comprising 238 cases, decidua

<sup>1</sup> From the Gynecological Service of Dr. I. C. Rubin, The Mount Sinai Hospital, New York.

was present in 97, 40.7 per cent. Goldblatt and Schwartz correlated the endometrial findings with the pregnancy test. In their series, eighteen cases revealed no decidual reaction; ten of these patients had positive Friedman tests. Of these, the endometrium was reported as proliferative in nine and secretory in one. All these patients complained of vaginal bleeding.

In cases of metrorrhagia the presence of a persistently positive pregnancy test, even without a pelvic mass or endometrial decidua is an indication for laparotomy. Following the completion of an intrauterine abortion, the pregnancy test may remain positive for a variable though usually brief period of time. Retained secundines or placental polyps may lead to a persistently positive pregnancy test, but these would probably yield to adequate curettage. Hydatid mole and uterine chorionepitheliomata would become evident on curettage. Rubin (1) reports a case of vaginal bleeding with a persistently positive Aschheim-Zondek test. The pelvic findings were normal and curettings on three occasions were negative. The pathological examination revealed a small intramural uterine chorionepithelioma. A mole had been removed four months previously. The pregnancy test, positive in a dilution as high as 1:50 before operation, was reported negative six days after hysterectomy.

#### CASE REPORTS

*History* (Adm. 485064): H. N. was admitted to the Gynecological Service of Dr. I. C. Rubin January 29, 1942. This was the first admission of a 34 year old, white, gravida 3, para 1, complaining of vaginal bleeding of five and one-half weeks duration. The previous menstrual history was normal with periods every 31-33 days. Her last regular period began on November 15 and lasted five days. The present episode of bleeding began December 22 and remained profuse with passage of large clots up to the time of admission. There was no associated abdominal pain.

On January 10 she was curetted at another hospital, but this procedure did not control the bleeding. The pathological report, as obtained from that hospital was, "hyperplasia of a secretory endometrium with pseudo-decidual reaction of the endometrial stroma. No chorionic villi were found." These slides were not available for study. A pregnancy test was not done.

There were no associated signs or symptoms of pregnancy. Her past and familial history were essentially normal. No history of adnexal disease could be elicited.

*Examination:* The general physical status was negative. The blood pressure was 110 systolic and 70 diastolic. The pelvic examination revealed moderate bleeding from the uterus, which was slightly enlarged and freely movable. The cervix seemed softened; the adnexa were neither palpable nor tender. No masses were noted.

*Laboratory Data:* Blood and urine examinations were within normal limits. The erythrocyte sedimentation rate was slow. The pregnancy test reported February 1 was positive.

*Course:* Because of the absence of palpatory evidence of extrauterine gestation, the positive pregnancy test and the persistent bleeding, a diagnostic curettage was performed on February 2.

*Pathological Report* (S-77857): "Endometrium in proliferative phase. No decidual reaction seen" (fig. 1). The pregnancy test was repeated on February 5 and the report was again positive.

*Operation:* Laparotomy was advised and performed on February 5. A right ampullary tubal pregnancy was found. A right salpingectomy was performed.

The pathology report (S-77898) was "tubal pregnancy."

*Post-operative Course* was uneventful. Prior to discharge a hystrogram revealed the uterine cavity to be slightly enlarged. The left tube was fairly well visualized and appeared to be patent.

*Case 2. History* (Adm. 510179): F. H. was admitted to the Gynecological Service of Dr. I. C. Rubin on September 4, 1943. This was the first admission of a 34 year old gravida 1, para 0, complaining of vaginal bleeding and lower abdominal discomfort for one week. Her menstrual history was normal until an operation for ruptured ectopic pregnancy two years prior to admission. Since then her periods had been profuse lasting for 8-10 days, where previously they were of 6-7 days duration. The last period occurred July 21-27. On August 27 vaginal staining was noted and persisted until September 2, when moderate vaginal bleeding with passage of clots began.

Two years before admission the patient had an episode of vaginal bleeding similar to the present. A dilatation and curettage for suspected incomplete abortion was performed at another hospital. The report of the curettings was, "endometrium in follicular phase. No evidence of decidua." The patient was discharged from the hospital only to return one month later with a ruptured ectopic pregnancy. There was no record of any pregnancy tests.

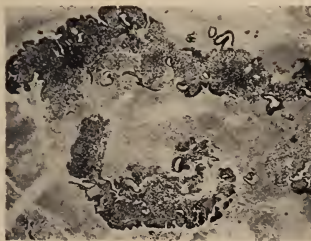


FIG. 1

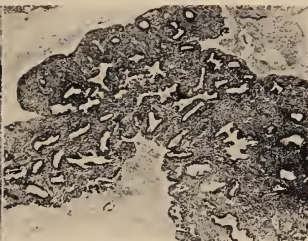


FIG. 2

FIGS. 1 AND 2. Photomicrograph of curettings showing endometrium in the proliferative phase. No decidual reaction is seen.

The patient volunteered the information that her present symptoms were similar in many respects to her previous illness.

There was no history of inflammatory disease of the adnexa. Contraception had not been used because the patient was eager to become pregnant.

*Examination:* The general physical status was negative. The blood pressure was 110 systolic and 60 diastolic. The pelvic examination revealed the cervix to be somewhat softened and closed. The uterus was anteverted, somewhat irregular and enlarged to the size of a six weeks gestation. There was moderate bleeding from the uterus. No adnexal masses were felt.

*Laboratory Data:* The urine was normal. The Wassermann reaction was negative. The erythrocyte sedimentation rate was normal.

A pregnancy test performed by an outside laboratory with a urine obtained September 4 was reported to be negative. Pregnancy tests at the hospital were positive on September 6 and September 9.

*Course:* The differential diagnosis rested between a threatened or incomplete abortion and an ectopic pregnancy in the right tube. The bleeding continued and a diagnostic curettage was performed on September 20.

Pathological report (S-83377): "Fragments of endometrium in proliferative phase" (fig. 2).

On September 23 a pregnancy test was repeated and again reported positive. Although the pelvic palpatory findings were unchanged, it was felt that the persistently positive pregnancy test made operative intervention advisable.

*Operation:* Laparotomy was performed on September 23 and a right unruptured tubal pregnancy was found. The right ovary containing the corpus luteum was adherent to the fimbriated portion of the right tube. The left ovary appeared normal. A right salpingo-oophorectomy was performed.

*Pathological Report (S-83411):* "Tubal Ectopic Pregnancy. Viable villi found. Ovary with corpus luteum of pregnancy and cystic follicles."

*Post-operative Course* was uneventful. Pregnancy test taken September 29 was reported as negative.

#### SUMMARY AND CONCLUSIONS

Both of these patients presented the problem of differentiating between an incomplete abortion and an unruptured extrauterine pregnancy where adnexae were not palpable. One of the patients had presented a similar episode previously. Curettage revealed proliferative endometrium without decidua. Repeated pregnancy tests were positive. It has been shown that these patients may be observed safely in a hospital. As soon as the existence of a viable intrauterine pregnancy is ruled out, a diagnostic curettage is justified. However, in the presence of bleeding, study of 238 cases reported in the literature showed no decidual reaction in 59.3 per cent. The decidual endometrium had probably been passed prior to the curettage. Perhaps the continuous bleeding inhibits decidual formation in the regenerating endometrium.

Where the endometrium shows no evidence of decidua, it is suggested that the pregnancy test be repeated 5-7 days after the curettage. With the persistence of a positive test, laparotomy should be performed even in the absence of pelvic findings.

We wish to thank Dr. I. C. Rubin for the privilege of reporting these cases.

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# THE DEVELOPMENT OF THE TECHNIQUE OF BLOOD TRANSFUSION SINCE 1907

WITH SPECIAL REFERENCE TO CONTRIBUTIONS BY MEMBERS OF THE STAFF OF  
THE MOUNT SINAI HOSPITAL

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The Editor of this Journal recently asked me to write a review of the development of the technique of blood transfusion during the last few decades.

For two reasons I take great pleasure in responding to his suggestion and to contribute this article to the Alfred Meyer Anniversary Volume.

1) Both Dr. Meyer and I, during our days of active service at The Mount Sinai Hospital, had the opportunity of observing the gradual simplification of the technique of blood transfusion.

2) Through my work in developing the citrate method I have been instrumental in transforming blood transfusion from one of the most complicated to one of the simplest and most useful procedures in our surgical armamentarium. I have fought for the popularization of the citrate transfusion for over twenty years. Naturally I am familiar with all the steps which led to the general adoption of this method.

The reader will forgive me for giving this article a personal note. I have weighed carefully different forms of presentation. However, the only logical form seemed to me to present my own observations from the early days of blood transfusion in this country to the present time.

In any proper evaluation of the different factors which have put blood transfusion on a safe basis, first place should be given to Landsteiner's epochal work on the identification of blood groups. This monumental paper (1), for which Landsteiner many years later (1930) received the Nobel prize, was published by him in Vienna in 1901. Though in his original article he suggested that the blood groups might be important for transfusion, group tests were not used in the early days of direct blood transfusion.

Landsteiner, the great scientist who spent his life in pure research, probably was not interested in, nor was he aware of, the great importance which his work would play years later in the wide employment of blood transfusion. Ottenberg deserves much credit for connecting Landsteiner's work with human blood transfusion. In 1907 (when still an interne at the German Hospital, now the Lenox Hill Hospital, in New York) he was the first to match donor and recipient before a blood transfusion (2). Looking back it seems incredible that six years should have elapsed, before Landsteiner's work was put to practical use. We may understand this delay, if we remember 1) that in the first decade of this century blood transfusions were very rare and 2) that direct blood transfusion was developed in this country. Forty years ago the foreign literature was not as easily available in this country as it is today. Landsteiner performed his re-

search on blood groups in Vienna at about the same time as Carrel (3, 4) and Crile (5) demonstrated here the feasibility of transfusing blood from donor to recipient by blood vessel anastomosis. Yet it took several years until blood grouping was used on patients, thus making transfusion a safe procedure. I wonder how many lives were either lost or put into serious jeopardy during these years, when blood transfusions were given without previous tests.

Why accidents did not occur more frequently than they did, was explained by Ottenberg (then on the laboratory staff of Mount Sinai Hospital) in 1911 (7). He showed that it was in practice safe to transfuse blood whose serum acted on the cells of the patients, but dangerous to use blood whose cells were acted on by the serum of the patient. This led to the widespread employment of group O (whose cells are inagglutinable) as a so-called universal donor.

It is interesting to point out and may appear incredible to our younger generation of doctors that the introduction of blood matching created a great deal of opposition. Many surgeons (in those days transfusions were a major operation and were performed by surgeons only) felt that these tests were unnecessary. Others opposed them as misleading. It seems that practically every progressive step in medicine has to be fought against strong and reactionary opposition.

For instance, I remember well—about 50 years ago—the strong opposition which Behring's diphtheria antitoxin encountered in its early days. In the same way Ehrlich met with the strongest antagonism from the medical profession, when he tried to introduce salvarsan. These two striking examples, taken at random, could be multiplied with greatest ease.

It is not within the realm of this paper to discuss in detail the technique and modern refinements of blood grouping. This chapter might be presented some day in this Journal by Dr. N. Rosenthal who has been in charge of the hematological department of The Mount Sinai Hospital for 25 years. Furthermore I do not consider my knowledge of the modern development in blood grouping as sufficiently authoritative to attempt a detailed discussion of the subject.

But let us now put the clock back 35 years and enter an operating room in which a direct transfusion is in progress. I take with me a member of the present house staff, a young man who has never seen any but the citrate method. To his great amazement he sees two operating tables placed side by side; the donor lies on one table, the recipient on the other. He sees the surgeon surrounded by three or four assistants. Two or three nurses pass instruments; among these instruments different sizes of artery clamps predominate. The radial artery of the donor is exposed and after a vein of the recipient has been dissected, both vessels are united with a Crile cannula, which made the transfer of blood from donor to recipient a safe, though technically a most difficult procedure. This cannula was introduced by Crile (5) in 1907 and had replaced suture of the blood vessels (Carrel).

It is impossible to describe the amazement of my young colleague. He does not believe his eyes. He is accustomed to collecting blood (either without any assistance or with the help of one nurse) in a flask in the dressing room of the ward (if he does not get the citrated blood from the blood bank) and bring it to

the bed of the patient where it is injected like any ordinary saline solution. But here he sees a major operation. If we stay from beginning to end, he will notice that the technical preparation of the operative field (including the establishment of the anastomosis) may last over two and sometimes three hours. The slightest motion of donor or recipient stops the proper functioning of the anastomosis or a clot may form, which makes useless all the difficult work of the surgeon. Many questions arise in the mind of my young colleague: 1) How can the surgeon define the exact quantity of transfused blood? Answer: He cannot. A hemoglobinometer serves as indicator of the rise of the hemoglobin in the recipient. Naturally this is a very uncertain method and cases of over-transfusion were not infrequent (Ottenberg and Libman (9)). 2) How can this method be used in cases of a sudden, profuse hemorrhage? Answer: This group of cases cannot

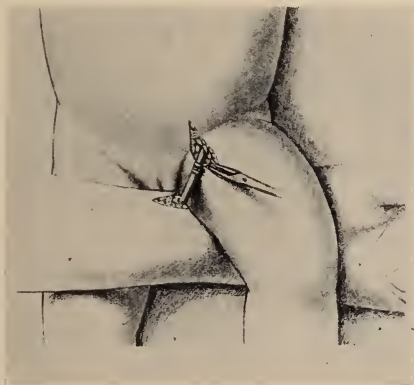


FIG. 1. Position of baby and the arm of the donor in direct transfusion. The radial artery of the donor and the femoral vein of the baby are used for the transfusion which is done according to the Crile technique (reproduced from Lespinasse, The treatment of hemorrhagic disease of the newborn by direct transfusion of blood. J. A. M. A. 62: 1866, 1914.)

get the benefit of transfusion. 3) How can this difficult method be made available to patients in smaller communities? Answer: It cannot. The direct transfusion requires a specially organized staff of doctors and nurses. 4) How can this method be used if an emergency (hemorrhage or shock) arises during an operation? Answer: It is impossible to give a patient the benefit of a direct blood transfusion during an operation. 5) Can direct transfusion be used in small infants? Answer: The technical difficulties are practically insurmountable (fig. 1). The differences in the size of the blood vessels of donor and recipient make an anastomosis most difficult. Furthermore the slightest motion of the infant may separate the anastomosis. 6) Ten to 15 blood transfusions are now often given to the same patient; would that be possible when using direct

transfusion? Answer: No, direct transfusion requires a dissection of a large vein of the recipient, thus making this vein useless for further blood transfusions; therefore patient cannot get more than two or possibly three transfusions. 7) How many direct blood transfusions are given every year? Answer: No exact figures are available, as the operating room books (with records of the operations) have been destroyed up to 1921. However, it is safe to say that not more than 50 (and probably considerably less) direct transfusions per year were given at The Mount Sinai Hospital between 1907 and 1914. But compare this figure with those of 1941. In 1941, 2907 transfusions were given at The Mount Sinai Hospital. Of these 2903 were given by the citrate method and 4 by the Unger method. I have tried to read some of the thoughts of my young friend, but I am sure that many others run through his mind.

This picture of the difficulties of direct transfusion is not the viewpoint of an observer watching from the sidelines. As adjunct surgeon to The Mount Sinai Hospital (1907-1914) I performed a few direct transfusions, some successful, others a partial or complete failure.

In 1908 Elsberg (6) (then Associate Surgeon to The Mount Sinai Hospital) simplified the technique by constructing a new cannula, based on the principle of a monkey wrench. His instrument gained considerable popularity.

As indicated in the title, this paper will point out the more important contributions to the progress of blood transfusion by members of the staff of The Mount Sinai Hospital. Now progress in any field of surgery is not confined to technique alone. Clinical studies and the evaluation of indications very often outrank purely technical improvements. If The Mount Sinai Hospital has contributed a fair share to the development of blood transfusion, it is in a large measure due to Libman (then associate physician at The Mount Sinai Hospital). Immediately after the publication of Crile's technique of vessel anastomosis with the aid of a cannula, Libman aroused the interest of the staff in this new field. This led to the introduction of new methods by members of the staff (Unger's method and the citrate method). A number of important papers (7, 8, 9, 10) on blood grouping and indications and management of blood transfusion were published by members of the staff between 1911 and 1915. The paper by Ottenberg and Libman (9) (Ottenberg had joined the medical staff at The Mount Sinai Hospital in 1908) represents one of the earliest and most comprehensive studies of the value of blood transfusion in clinical medicine. In this excellent paper 212 transfusions (a considerable number for those days)—192 performed by the direct method—were reported and properly evaluated by them.

Direct blood transfusion reigned supreme between 1907 and 1913, a very long period considering its difficult technique, its limited usefulness and the impossibility of measuring accurately the quantity of the transfused blood. Many of these difficulties were overcome when Lindeman (11) introduced the syringe method in 1913. In 1894 Ziemssen (12), then professor of medicine in Munich, had used the syringe technique for transfusion. However, in those years transfusions were so rare that the method was completely forgotten.

The syringe method was a great step forward towards simplification of the

technique of blood transfusion. After the ball had started rolling, this process of simplification proceeded very rapidly. Two years later it found its final solution in the citrate method.

The great advantages of the Lindeman technique over the direct transfusion were very obvious. No dissection of blood vessels was necessary either in donor or recipient. Thus the same blood vessels could be used again and again both in donor and recipient. The exact quantity of transfused blood was known. Donor and recipient, while in the same room on operating tables next to each other were completely separated during the transfusion.

The remaining disadvantages even of this simplified technique were that transfusions could not be given during an operation; the transfusion required a staff of two well-trained doctors and two well-trained nurses; the method was expensive as it required a large number of 20 cc. syringes, the syringe method made a rapid injection of the blood mandatory, thus possibly causing an unnecessary and harmful overloading of the circulation.

Some of these difficulties were overcome when Unger (1915) (13), (then a member of the house staff of The Mount Sinai Hospital) devised an apparatus based on the principle of the two-way stopcock. This apparatus became very popular and was used extensively for many years.

Other apparatus (Kush, The Mount Sinai Hospital, 1915 (14); Bernheim, Baltimore, 1915 (15); Oehlecker, Hamburg, 1919 (16); Tzanek, Paris, (17); and Hirsch, The Mount Sinai Hospital, 1935, (18)) are based on a technical principle similar to that of the Unger machine.

In all these variations of the Lindeman technique 20 cc. record syringes were used. It is a well known fact that after the syringe has been used two or three times for aspiration and injection of the blood the piston fails to work properly. It is generally assumed that two factors are responsible for this—early stages of coagulation of the blood and the heating of the piston in the syringe. To overcome the first, Lindeman provided for a thorough cleaning of each syringe on its way from recipient to donor. To provide against the heating of the piston he immersed the syringes in ice-water.

Elsberg showed that both these factors can be overcome by a very simple device. He proved experimentally that an ether-spray will insure the steady and safe working of one syringe in connection with an Unger apparatus, even if used in large transfusions. He suggested to Unger to chill with an ether spray the outside of the syringe during aspiration and injection of the blood. Thus Unger could reduce the number of syringes, used in connection with his apparatus from 4 to 2, which materially simplified his method.

Probably about 100 varieties of syringe based on the two-way stopcock principle were constructed between 1915 and 1930. It would be impossible to mention them here, especially as all syringe methods are of historic interest only. Even apparatus driven by electricity were placed on the market.

Lindeman described his syringe cannula method in 1913. In the same year Kimpton and Brown (19) presented their method which collected the blood in large (250 cm.) paraffinized glass cylinders. The smooth surface which the

paraffin effected on the inner side of the glass cylinders prevented coagulation of the blood, at least over a considerable time. Thus donor and patient could be in adjoining rooms, not side by side (as in the direct method or the different varieties of syringe methods). The shape of the glass cylinders was modified by Percy (20), then associate of Albert Ochsner at the Augustana Hospital, Chicago. In its original form this method required a dissection of the veins of both donor and recipient. Vincent (21) overcame this objection by attaching a cannula with a piece of rubber to the glass cannula.

In a paper which I presented in Boston in 1924 (36) I pointed out that the proper coating of the glass cylinders required considerable experience and skill. It cannot be described clearly. It must be shown and explained in detail. For this reason it did not acquire great popularity. This method travelled all the way to Europe where it was used in a number of clinics. In those days Clairmont's clinic in Zürich and Ochsner's service exchanged internes. These young men brought the technique of the paraffinized glass cylinders to Switzerland, when they returned from their post-graduate course. Thus the Percy modification of the Kimpton-Brown method was very popular at the University Clinic in Zürich whence it found its way to other hospitals on the continent.

In order to do away with the difficulty of the proper paraffinization of the cylinders Neubauer and Lampert (Munich) (22) in 1930 constructed glass cylinders made of amber. It is well known that the surface of amber is exceedingly smooth. Thus coagulation of the blood will not occur in the brief period of the transfer of blood from donor to recipient.

It must be perfectly clear to the reader that not only the direct transfusion was technically a most difficult method, but that even the syringe methods and the glass cylinder technique lacked sufficient flexibility to make them available for general use.

While many doctors hailed the syringe technique as the final solution of the problem of blood transfusion it seemed to me that the technique should be further simplified, if blood transfusion was to be made available to anybody who might be in need of it. It was perfectly evident that the only reason for the complicated methods heretofore in vogue was the fact that human blood clots outside the body in 3 to 5 minutes. If it were possible to retard the rapid coagulation of the blood, transfusion could be performed with the greatest ease, without undue hurry and without acquiring any special technical skill.

The only logical solution of this problem was the use of anticoagulants and I recall discussing it with one of my colleagues at the hospital and saying, "If I could mix the blood with an anticoagulant, I could collect the blood on the medical service of the hospital and carry it over to the surgical service for injection." This suggestion seemed to him quite a revolutionary idea. Gradually the problem became clearer in my mind. In my first extensive paper on the subject of citrate transfusion (1915) (27) I find the following paragraphs:

"Any transfusion in which the normal coagulation time of the blood is considered as an unalterable factor, is apt to be difficult and apt to require a great deal of personal experience and skill. Must we accept this coagulation time as

an unchangeable law? Might it not be possible to inhibit the danger of the clotting of the blood during its transfer without diminishing the clinical value of the blood for the recipient? This was the problem to be worked out and it seemed to me that this problem would be worth a thorough and careful investigation. If solved, blood transfusion, which so far has given only good results in the hands of a limited number, would be changed from a very complicated and difficult method to one of greatest simplicity. Special clinical skill and experience for this work would no longer be required, no haste would be necessary in the performance of blood transfusion, in short blood transfusion would be technically as easy as an ordinary saline infusion.

"The problem then was to find a chemical substance which would retard the coagulation of the blood for at least thirty minutes, so as to guarantee a safe transfer of the blood without any haste. Furthermore this substance had to be conditionally atoxic, so that large transfusions of blood (up to 1500 cc.) could be performed with perfect safety."

I have quoted these two paragraphs from a paper written by me 28 years ago in order to show that I had a very clear picture and a precise working plan before I started the experimental work which led to the establishment of the citrate method of blood transfusion.

I started the work with anticoagulants by using hirudin. I soon found that hirudin was much too toxic for intravenous use in human blood transfusion. A number of anticoagulants had been used previously by different authors in blood transfusion, namely sodium citrate, sodium oxalate, sodium bicarbonate, sodium phosphate, glucose solution, etc. The famous obstetrician Braxton Hicks (London) (23) used sodium phosphate as far back as 1869 in a number of blood transfusions on seven patients. They all died. His early attempts to use an anticoagulant in blood transfusion were forgotten completely. Wright (24) gave oxalated blood to three dogs without any harmful effect.

It is clear from these references that long before the present era of citrate transfusions others tried to accomplish the same end. Even sodium citrate had been considered for this purpose. For instance Lespinasse (25) in closing the discussion of his paper on direct transfusion of blood read before the Chicago Medical Society, April 29, 1914 stated, "In 1908 and 1909 I canvassed that problem (use of anticoagulants) rather thoroughly and found the peptone and hirudin absolutely toxic; the sodium citrate in moderate amounts is quite toxic, in smaller amounts it is not so toxic. But it is toxic. In the hemorrhagic cases, such as that of a baby reported in my paper, any method that includes a non-coagulating element in the transfused blood is absolutely contraindicated." We shall see later that this last sentence in Lespinasse's discussion was much too general. Sodium citrate loses its anticoagulating quality as soon as it enters the blood stream.

Most of the progress in clinical medicine has been based on preliminary careful animal experiments. Ehrlich tried 605 different chemical compounds, until he produced salvarsan (606). Whipple had laid the basis for the treatment of pernicious anemia in a series of animal experiments, before Minot and Murphy

applied this work to patients. Banting's and Best's long and careful experimental work on insulin is another example of the proper approach to a new problem in clinical medicine.

I shall not review in detail reports of the experiments which we (Dr. George Baehr, then on the laboratory staff of the hospital, most ably cooperated with me in the planning of the experiments) carried out on dogs in the fall of 1914. My early papers (26, 27) give all the data of these experiments. Suffice it here to summarize the main results:

(1) 0.2 per cent is the percentage of sodium citrate and blood required for the safe prevention of coagulation.

(2) 5 Gm. of sodium citrate can be introduced safely into an adult. Larger amounts are toxic. We rarely transfuse more than 1,000 cc. of blood at one transfusion, which would represent 2 Gm. of sodium citrate. However, even a transfusion of 1500 cc. of blood would require not more than 3 Gm. of sodium citrate, a perfectly safe dosage.

The importance of these experiments will be apparent, if we bear in mind that a 1 per cent mixture of sodium citrate and blood had always been considered essential to prevent blood from clotting. Nobody had ever followed the simple thought of carrying out experiments to ascertain whether a much smaller dose might not be sufficient for the purpose. In a transfusion of 1000 cc. a 1 per cent mixture of sodium citrate and blood, representing 10 Gm. of sodium citrate would have been very toxic, whereas 0.2 per cent representing 2 Gm. is far below the limit of toxicity. Even 0.3 per cent can be given safely in a transfusion of 1500 cc. (representing 4.5 Gm. of sodium citrate), especially since the introduction of the intravenous drip. This is the dose which is usually given at present.

(3) The introduction of citrated blood causes a temporary shortening of the coagulation time of the recipient's blood. This coagulation time returns to its pre-transfusion level within a few hours.

How beautifully this drug responds to human needs! If the average transfusions were 3000 cc. instead of between 500 and 1000 cc. sodium citrate could never have been used on account of its danger to the patient.

Furthermore these experiments clarified a most important question as to whether infusion of citrated blood would lengthen the coagulation time of the blood of the recipient. If that had been the case, citrated blood would have had a very limited application. It could not have been used in cases of hemorrhage (for instance from a bleeding gastro-duodenal ulcer), in postoperative treatment or in the large group of hemorrhagic diseases. As it happens the citration does not change the coagulation time of the recipient (except for a rapidly passing initial shortening—a beautiful and most interesting phenomenon).

Before leaving this brief discussion of the experimental work I would like to point out that the level of the anticoagulating factor of sodium citrate lies between 0.14 and 0.15 per cent. A mixture of sodium citrate with blood at the ratio of 0.14 per cent will not prevent coagulation, whereas 0.15 per cent will keep the blood in fluid condition just as well as the higher values 0.2 per cent, 0.3 per cent or even 1 per cent.



FIG. 2. Complete outfit for transfusion of citrated blood



FIG. 3. Taking blood from the donor

I shall not discuss in detail the technique of the citrate method of blood transfusion, as I have frequently referred to it in previous papers. The accompanying pictures (the drawings were made many years ago) (figs. 2-4) show its

simplicity. It is still used today at The Mount Sinai Hospital in practically the same way as I devised it originally; the only change was the addition of a glass piece for the drop technique. Naturally when bank blood is used the open container is substituted by a closed bottle. Many other points of great interest in



FIG. 4. Infusion of citrated blood into the recipient

connection with the citrate method of blood transfusion cannot be discussed here. The reader is referred to my previous publications on this subject (26-38).

Any progressive step in medicine (or for that matter in many other branches of science) will usually be followed by an argument on priority. The citrate transfusion was no exception. I have discussed in detail in previous papers the claims of others. I shall summarize the facts very briefly.

Agote (Buenos Aires) (39) should get proper credit. His paper appeared at

exactly the same time as my original communication (January, 1915). He had the right percentage of sodium citrate (0.25 per cent). He reported 2 transfusions of 300 cc. each. He did not answer the question whether transfusions of average size (500 to 700 cc.) could be given with this method without causing toxic effects. Furthermore, he did not study the effect of anticoagulants on the coagulation time of the recipient. I have often said that when an idea is ripe it frequently occurs simultaneously to more than one person. Thus Agote and I in different and far distant parts of this hemisphere, hit upon the right technique at the same time.

The same cannot be said about Hustin and Weil.

Hustin's publication (40) antedated Agote's and my publications by a few months (April, 1914). Neither Agote nor I knew about Hustin's publication in a Belgian medical paper, as the foreign literature was inaccessible during the World War. However, Hustin did not solve the problem of citrate transfusion. He made the error of assuming that in order to prevent coagulation he had to mix the citrated blood with equal parts of glucose solution. Glucose has some anti-coagulating qualities (see above). Naturally, if Hustin's conclusions had been right and if his advice had been followed, citrate transfusion would never have made the grade. No doctor would have advised, in cases of hemorrhage, the administration of 250 cc. of strongly diluted blood according to Hustin's method, if he could give 500 cc. of undiluted blood according to the Lindeman or Kimpton technique. The same argument would have been brought forward against Hustin's technique in hemorrhagic diseases.

Hédon (41) in Montpellier (1917) summed up the situation very clearly: "Hustin mixed in equal parts blood with isotonic glucose-salt solution, containing a certain proportion of sodium citrate and injected this mixture in small quantities. Hustin's method of transfusion is really an infusion of strongly diluted blood mixed with citrate of soda and glucose."

Wiener (42) fully agrees with Hédon, by stating in his recent book (1943): "Citrated blood was used for the first time by Hustin in 1914 but his method consisted in infusing highly diluted blood mixed with sodium citrate and dextrose. At the beginning of 1915 Agote and Lewisohn simultaneously described the transfusion of citrated whole blood, but Lewisohn worked out the technique in detail, especially the amount of citrate to be used as an anticoagulant. Because of its simplicity, the method was used extensively during the first World War."

Undoubtedly Hustin was the first to use sodium citrate in a human blood transfusion. But Hustin applied it in the wrong way and thus failed to solve the problem.

Another contestant was Weil (43). He used a 1 per cent mixture of sodium citrate and blood; in other words, the same mixture which had been the standard mixture in laboratory work. As far back as 1916 Brem (44) administered 1 per cent citrated blood, as suggested by Weil, to nine patients and stated, "Weil's dose is toxic, dangerous and unnecessary." Furthermore Rous and Turner (1916) (60) found that human blood when mixed with sodium citrate at the rate of 1 per cent according to Weil's directions begins to hemolyze in about one week,

the hemolysis being more dangerous, because it is often completely concealed amid the sedimentation corpuscles. Weil observed the shortening of the coagulation time in the blood of the recipient following the injection of sodium citrate.

It was my good fortune to conceive the original apparatus in the most simple form. As a rule, a new method is originally conceived in rather complicated form and gradually simplified. With the citrate method of blood transfusion the sequence of events worked differently. Ever since I presented a technique of utmost simplicity in 1915, the profession has tried to complicate it by constructing or using more complicated apparatus. The main attack was made against the so-called open method. It would be interesting to reproduce here all the complicated apparatus which have been suggested and used (mostly by their authors only), during the last 25 years.

In order to prevent the confusion which might be caused by all these modifications of my original technique I suggested the name "citrate method" which is used to this day. To quote from one of my papers (32) published in 1919, "It seems advisable to adhere to the original name suggested by the author of this paper, 'citrate method.' Otherwise we would in a very short time have the same method called by a dozen different names according to different apparatus used in its execution. As stated above, the important principle is the application of sodium citrate; modifications of apparatus are of minor importance."

All these complicated apparatus are forgotten now with the possible exception of the vacoliter bottles. They seem still to be used quite extensively due to a widespread advertising campaign. An ordinary cheap open salvarsan flask (fig. 2) is as good as the expensive vacoliter bottle.

Adherents of the so-called closed method claimed that the open method might carry infection through the air to the recipient. It is perfectly obvious that this criticism is purely theoretical and not based on fact. May I remind the reader that any brain operation is an open method. If meningitis should occur, it is due to the faulty technique or sterilization, not to the fact that parts of the brain are exposed over a long period.

I remember very well the surprise of my colleagues when this method was published in January 1915. They could not believe that the technique of blood transfusion which had been so very complicated up to then, was suddenly made as simple as an ordinary saline infusion. I was invited by a number of hospitals (among others Presbyterian Hospital, St. Luke's Hospital, Roosevelt Hospital, Lenox Hill Hospital (then German Hospital), Post Graduate Hospital, Fordham Hospital and Lebanon Hospital) to demonstrate the technique. Naturally I thought that the safe and simple sodium citrate method of blood transfusion would be adopted universally and that the other methods would be discarded. However, the course of events was very different. Most hospitals in New York continued for many years to use the syringe methods (either Lindeman, Unger or some other technique). Even at The Mount Sinai Hospital the medical services and one of the surgical services continued to use the Unger method for many years.

I think there were two chief reasons which made the hospitals persist in using

the more complicated methods: 1) In each hospital one or two doctors had acquired the facility of performing a syringe transfusion. Naturally they objected to the introduction of a new technique which did not require the ability of a specialist, but could be performed with greatest ease by any member of the staff; 2) the fact that in the early years of citrate transfusion post-transfusion chills were more frequent following citrate transfusions than after transfusions of non-citrated blood.

It is difficult now that the citrate method of blood transfusion is the only surviving technique, to picture the criticism and objections which were brought forward against it. It is impossible to quote here the different authors who attacked and criticized the method. We could fill pages with these quotations. For instance, Unger (45) (1921) claimed that sodium citrate had a deleterious effect on the fragility of the red blood cells and that it decreases the phagocytic power of the leucocytes. Brines (1926) (46) stated, "The theory advanced a few years ago that the transfusing of unmodified blood is the most beneficial to the patient has now become a well established fact. Any attempt to retard coagulation by the addition of drugs impairs the value of the blood from a biologic and immunologic point of view to say nothing of the bacterial contamination usually accompanying the process of preventing coagulation." In an editorial in the *Journal of the American Medical Association* (1923) (47) entitled "The Status of Blood Transfusion" we find the following statement, "While the latter (citrate method) should not be abandoned, the whole blood method should, whenever possible be substituted for it; however, there is never a time when citrated blood is as good as whole blood."

It seemed that post-transfusion chills were more frequent following citrate transfusions than following syringe transfusions. The supporters of the syringe technique accused the sodium citrate. I always felt quite sure and have stated frequently that the sodium citrate could not be the cause of the chills. Many blamed the rubber tubing. Others starved either the donor or recipient or both before the transfusion. Some authors blamed the cooling of the blood during the infusion and constructed complicated and expensive electrical apparatus to keep the blood at a uniform temperature.

After all these different theories had been discussed for years Rosenthal (36) (hematologist to The Mount Sinai Hospital) showed that the post-transfusion chills were due first to foreign protein reactions and secondly to defects in the distillation of the water. Careful cleansing of instruments, tubing and glassware immediately after the transfusion is essential. Rosenthal with Miss Koch, one of our nurses, worked out a detailed technique for the safe and thorough removal of old blood which causes the pyrogenic reactions. He stressed the importance of the use of triply-distilled water.

Rosenthal's contribution was of the greatest importance for the popularization of the citrate method of blood transfusion. Regulations for the preparation of instruments for intravenous therapy were published in 1933 (36). Under Rosenthal's guidance a new department was created at The Mount Sinai Hospital, the first of its kind, the so-called department for intravenous therapy. All

the instruments used in intravenous therapy are returned immediately after use to this department and carefully cleansed and sterilized. Dr. Joseph Turner, director of The Mount Sinai Hospital, constructed a metal box for the sterilization of the gravity flask, rubber tubing and cannulas. This box is most popular and in universal use.

Immediately after these new regulations were introduced by Rosenthal, the percentage of chills following citrate transfusions at The Mount Sinai Hospital dropped from 12 to 1 per cent. It has stayed between 1 and 2 per cent all these years. An even more remarkable drop was observed by Satunov (Novgorod, Russia) (48), namely from 53 to 2 per cent. With the marked reduction of chills the citrate method began to forge way ahead of all the other methods. At present it reigns supreme.

Even this battle for the prevention of chills was not won easily. For instance, after our publication (38) Elser and Stillman (49) published a paper entitled, "The Fetish of Triply Distilled Water." Others claimed that these minute regulations for proper preparation of instruments were unnecessary. However, Rosenthal won right along the line. Like so many other problems, it appeared extremely simple—after he had solved it.

In the first year (1915) we had some trouble in keeping the citrate solution clear. It turned cloudy after a few weeks. However, since we have introduced the use of alkaline free—so-called Jena-glass, the citrate solution can now be kept indefinitely in perfect condition. I still have in my medicine closet an ampoule which Parke, Davis & Co. made for me in 1917. The citrate solution has kept perfectly clear all these years.

For many years many authors have grouped all the methods which did not use sodium citrate as methods using "pure" or "whole" blood. I have always claimed that citrated blood is just as pure as non-citrated blood. Time has proven that I was right. If citrated blood were not pure, it would not now be the method in general use. The title "whole blood" has now been transferred from the syringe methods to the citrate method, in order to differentiate citrated blood from citrated plasma. Time marches on!

Most writers on the subject of blood transfusion used to group together vessel anastomosis, the different syringe methods and the glass cylinder technique as direct methods and reserved the title of indirect method for the citrate method. I have stated repeatedly in my papers on this subject that the only "direct" method was the vessel anastomosis. "Direct" blood transfusion means that the blood does not leave the circulatory system during the transfer from donor to recipient. With the syringe methods, with the glass cylinder technique, and with the citrate method the blood leaves the circulatory system during the transfer from donor to recipient for shorter or longer periods. Thus it is clear that all these methods are indirect methods. It is difficult to understand how for years and years this erroneous classification continued, in spite of my strong and repeated protests.

The only change in the administration of a citrate transfusion since its original introduction 28 years ago is the change from a rapid infusion of the blood to the

slow drop method. The slow drop infusion of saline and glucose solution was used by Matas (50) and Friedemann (51) about 30 years ago. Undoubtedly this technique safeguards the patient against a sudden overloading of the circulatory system. Why the intravenous drip method was not generally adopted immediately after their publications is one of those riddles, which is impossible to answer. The intravenous drip for infusion of glucose solution and citrated blood has been used at The Mount Sinai Hospital since 1927. The drip method was popularized in this country by Hyman (then associate physician to The Mount Sinai Hospital) (52).

We have come to the end of this review. I have tried to present to the reader the development of the technique of blood transfusion as I have observed it during the last 36 years. But a few words are desirable without going into a detailed discussion, on the development of the blood banks and the plasma transfusion. They are outgrowths of the citrate method. The blood bank is not altogether new. It was used in World War I. The first blood bank in a general hospital was organized in Leningrad by Filatov and Doepp in 1932 (53). However, its general adoption is of a more recent date. It may be of interest to point out that Rosenthal at The Mount Sinai Hospital established the first blood bank in New York City in 1938 (54). Naturally neither blood nor plasma can be stored without the addition of sodium citrate.

Nor is the idea of plasma transfusion of recent date, as many authors on this subject seem to think. Space does not allow to quote the experiments which Rous and Wilson (55) performed on rabbits in 1918. In a report of the medical research committee (1918) Robertson (56) states: "Rous and Wilson have recently brought forward some further data on fluid substitutes for blood. They were able to show that after rabbits had been bled as much as three quarters of their total volume the blood pressure could be restored to normal by the immediate injection of an equal quantity of blood plasma freed from the red corpuscles. This improvement was maintained, and the animals remained in good condition through anemic. Six per cent gum acacia worked as well in these experiments as blood plasma."

In a very interesting letter to the British Medical Journal (1918) Ward (57) suggested plasma for the treatment of wounded in casualty clearing stations. He presented the problem in so clear and concise a way that I would like to reproduce his letter:

"Sir,—I have been reading with interest recent articles in the Journal on blood transfusions in casualty clearing stations. Apparently one of the chief troubles is the question whether or not the recipient's plasma will hemolyze the corpuscles of the donor.

"Surely this difficulty might be avoided by not transfusing the corpuscles at all, but only citrated plasma, which would be easy to keep and easy to give. There is abundant clinical and experimental evidence that it is not the corpuscles that are wanted, but the ideal fluid for keeping blood pressure at its proper level, and the apparent advantage of blood is, no doubt, due to its permanent value in this respect and to its food value. A man apparently dying from hemorrhage is not dying from lack of hemoglobin, else severe cases of anemia would die long before they do, but from draining away of fluid, resulting in devitalization and low blood pressure.

"May I at least recommend a trial of this method, controlled, let us say, by an equal number of whole blood transfusions and an equal number of gum acacia (not less than 6 per cent) cases?—I am, etc.

GORDON R. WARD  
Captain R.A.M.C. (S.R.)"

It would seem that this suggestion lay dormant for 15 years. In 1933 Filatov and his co-workers (58) used plasma extensively in cases of burns and shock. They found that plasma can be stored for many months. The plasma bank was popularized in this country by Strumia (59).

The great advantage of the citrated plasma transfusion is the fact that grouping of donor and recipient is unnecessary. Thus it is eminently fitted for immediate action on the battlefield in cases of severe shock and extensive burns. However, the great enthusiasm for plasma seems already somewhat on the wane. For instance, Colonel Churchill (the well-known Boston surgeon, at present in North Africa) stated recently, "There is need for whole blood transfusions in the treatment of a significant portion of the wounded. Plasma is not an adequate substitute in these cases."

During the last war (1918) Robertson reported transfusion with preserved red blood cells, a method which has been revived recently. In his very interesting paper he quotes the experimental work of Rous and Turner (60). They showed in rabbits that it is possible to preserve red blood cells for several weeks in a solution of dextrose and citrate when kept at ice-box temperature. Robertson (61) gave transfusions of preserved red blood cells at casualty clearing stations during a rush period. A quantity of blood was stored up beforehand ready when needed. The blood was kept for varying periods up to 26 days before transfusion.

Plasma and red blood cells suspensions may be used in an emergency. However, they will never fully replace whole blood. After all they represent only certain parts of the blood constituents and thus lack the biological value of whole blood.

Is it not remarkable that so small an addition to our knowledge, namely, that sodium citrate mixed with blood at the rate of 0.2 per cent instead of 1 per cent prevents coagulation of the blood, made possible citrated blood and citrated plasma transfusions thereby saving so many lives in peace and war?

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COLEY'S MIXED TOXINES OF ERYSIPELAS AND PRODIGIOSUS  
REPORT OF TWO CASES OF INOPERABLE SARCOMA TREATED BY COLEY'S METHOD

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PREFATORY NOTE ON DR. MEYER

Fifty-seven years ago I first met and admired Dr. Alfred Meyer as a physician and as a friend. His kind, sympathetic and skillful service rendered in my own family will always be gratefully remembered.

Our acquaintance began soon after my entering The Mount Sinai Hospital as an intern late in 1886.

One day, sitting at the table in the reception room for the Attendings on their visits to the hospital, there appeared a brisk yet dignified medical man, promptly greeted by the House Physician who, rising with respect, presented himself for service. Of course I, too, rose, wondering who this blond-bearded young man might be and I was introduced by Dr. E. J. Ware, the "House," to Dr. Alfred Meyer. He casually returned my salute and with agile steps led the way to the medical wards, leaving me to my meditations. He didn't seem any older than I, just out of the medical school.

As I became better acquainted with Dr. Meyer, he impressed me more and more. His manner of examining a new patient held one's attention. I'll not attempt to describe his quick but convincing motions, his top-to-bottom going-over of the patient beginning with the head and ending with a minute inspection of the toe-nails; his thoroughness was invariably convincing.

My term of service was, at last, finished and, in the early years of practice the younger medical men occasionally referred problem cases to me for an opinion or even for operation. When some one came bringing a note of introduction from Dr. Meyer it was a genuine compliment and an indication to me that I was about to Arrive.

Most of these patients were from his general practice and recently on going over my records I found more than thirty. It was not until years later that he became the distinguished figure which has marked his life, in Thoracic Medicine.

\* \* \*

Two cases of malignant tumor treated by the toxines of erysipelas and bacillus prodigiosus (Coley's fluid).

*Case 1.* Henry B., a merchant, aged 48, came to me from Dr. Meyer on November 13, 1901. His history had been irrelevant until about nine months before when he began to suffer pain in the axillary line of the left chest-wall and a sausage-shaped swelling appeared involving the seventh and eighth ribs; the visible tumor had been noted only about five weeks before the visit and there had been loss of body-weight almost from the beginning. Medical treatment including the administration of iodide of potassium had been without avail.

On examination the mass was about five inches in length; it was elastic and yielded a crackling sensation, occasionally noted in sarcoma and, rarely, in tuberculous swelling of bone. No cough or other respiratory phenomena were present.

Thirty years ago x-ray examination was by no means as accurate as today so it is hardly surprising that we were unable to add anything material to the diagnosis and exploratory incision was therefore advised.

Mr. B. entered the private pavilion of The Mount Sinai Hospital and two days after my first examination the operation was performed under nitrous oxide anesthesia.

*Procedure:* An incision eight inches long was made over the seventh rib and parallel with it but not, at first, invading the bone. Needle aspiration through the depths of the wound withdrew blood-stained serous fluid with no coagula. On further exploration the pleura was entered for digital examination but nothing abnormal was found.

A section of the chest-wall with ribs, pleura and muscle was taken away and another smaller cyst higher in the parietal thorax was discovered and also excised. The wound was sutured leaving room for gauze drainage which was extracted two days later.

Healing was primary and prompt recovery followed with great relief of the symptoms. On November 27, only 12 days after operation the patient was discharged as "improved."

Dr. F. S. Mandlebaum, our pathologist, reported that the specimen was melanotic. "The tumor is a pigmented sarcoma of the mixed fibromatous type; the prominent feature of the tumor is the infiltration of the sarcomatous tissue by pigmented cells."

I insisted that Mr. B. should come frequently to my office and a few weeks later thickening of the scar, especially at its extremities indicated recurrence in the bone which forbade further operative procedure. However, I had seen good results and even recoveries in sarcoma, though not of the melanotic variety, following treatment by injections of the mixed toxins of erysipelas and bacillus prodigiosus (Coley's fluid) and it was decided that this form of therapy should be carried out, without the patient's residence in the hospital.

Daily inoculations were made into the region of the recurrence, beginning with half a minim and gradually increasing the dose. The patient kept records of his body-weight and temperature as well as his subjective sensations and, from the beginning although there was elevation of temperature, he felt that he was improving. When a single dose of eight minims had been administered it was followed by a chill and high temperature so that the quantity was reduced and yet, in spite of continued injections there was general amelioration to an astonishing degree, with rapid decrease in the size of the tumor. The therapy was continued as long as there was *general* improvement even for a time after all trace of the tumor had disappeared and normal health had returned.

On December 10, 1902, I presented Mr. B. before the New York Surgical Society, apparently perfectly normal and weighing more than he ever had.<sup>1</sup> He remained well for about nine years when he died of a disease not associated with new growth.

*Case 2.* (Not from the practice of Dr. Meyer, but even more amazing than that of Mr. Henry B.). A girl, aged two years, Phyllis H., who was brought to me by Dr. Alfred W. Pollak and in 1927 was presented before the Surgical Society.<sup>2</sup> I shall here give only a brief report.

<sup>1</sup> Ann. Surg., 37: 440, 1903.

<sup>2</sup> Ann. Surg., 85: 615, 1927.

She was completely paraplegic because of the extension of a mediastinal tumor into the spine. An exploratory operation with rib resection had been performed opening the right mediastinum and disclosing a large inoperable tumor. A specimen of considerable size was removed and submitted to Dr. Mandlebaum who made a report of Angiosarcoma, not pigmented. Two years later, Dr. Gross, then Director of the Laboratory, reported on the same specimen as hemangio-epithelioma, not pigmented. Two years later, following



FIG. 1

treatment by Coley's toxins, x-ray examination (Jaches) failed to reveal a tumor of any kind.

I presented a microscopic slide of the tumor to the late Dr. James Ewing and from his dictation I wrote the following: "Malignant cellular tumor of embryo type, composed of many blood-sinuses lined by two or more rows of tumor cells. Very delicate stroma." He considered the tumor extremely malignant.

By this time the patient had been treated by Dr. Pollak using, at my suggestion, Coley's method; at 14 years of age she appeared before the Surgical Society walking normally and with no deformity visible. A series of roentgenograms

were negative. Those interested may consult the *Annals of Surgery* for December 1936. Today, August 14 1943,<sup>3</sup> Phyllis called upon me at my residence and I found her *well* and exceptionally active at the age of 21. The thoracic scar was in the soft parts of the upper right thorax only. She does clerical work and is interested in the matters which concern young adults; incidentally, she is an attractive girl (fig. 1).

The influence of erysipelas in certain malignant growths was first brought to the notice of the profession by Sir James Paget in one of the volumes of *Clinical Lectures and Essays*, but the effect was noted in patients who contracted the disease, and in this case the erysipelas might become uncontrollable. It was not until William B. Coley made experiments with the toxins of erysipelas instead of the living germs that the method began to assume a practical form. Later, Coley found that the addition of the toxins of *bacillus prodigiosus* increased the effects of the injections. The method is especially desirable when the tumors are inoperable.

A book is in preparation by Dr. Walker E. Swift, of New York, with whom are associated Helen Coley Nauts, the late Dr. Coley's daughter, and Colonel Bradley L. Coley, M.C., now in the United States Army Service. It is contemplated by the writers of this work to give the entire history of the subject, the names of the various manufacturers of the fluid both in this country and abroad, together with full details of its preparation and administration.

There will also be reports of about six hundred cases.

From my own experience I feel convinced that in the near future, treatment by Coley's toxins will be given a fair trial. It is probable that the discontinuance of the toxine treatment may have been partly due to roentgen-ray therapy and the discovery of radium. The toxins have the advantage of acting in generalized tumors even when there are distant metastases which could not be reached by x-ray or radium.

<sup>3</sup> This date refers to the time the article was completed and submitted for publication.

## ISAAC WALLACH AND THE MOUNT SINAI HOSPITAL

MORRIS MANGES, M.D.

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For fifty years I have enjoyed the association with Alfred Meyer as a friend and as a colleague I wish to join his many other friends in this tribute celebrating, somewhat in advance, his ninetieth birthday.

Tradition, though deeply rooted in The Mount Sinai Hospital, needs occasional awakening. Of the many doctors, nurses and patients who daily enter its foyer, now or then, one may glance at the broad marble staircase and then perhaps look upward to the large, splendid bronze bust with the inscription, "Isaac Wallach, Erected in Grateful Recognition of his Services as Director and President, 1877-1907." What memories does that arouse from the forgotten past?

Isaac Wallach was born in Bavaria in 1839. When he was three years old his parents with a large family settled in Hartford, Connecticut. Seven years later they moved to New York City, which became their home for the rest of their lives. He was educated in the public schools and then was employed in his father's thriving business in cotton goods. He and his older brother, with whom he was associated for many years, were very successful as cotton convertors. As a young man he married Hannah Frank who bore him a son and four daughters, all of whom died except one daughter.

With only the meager public-schooling of that day he later accomplished much as evidenced by the splendid style of his letters, messages and annual reports, as well as his public speaking.

Early in his career he joined the several charitable societies of that day, but he displayed an especial interest in The Mount Sinai Hospital. He was elected as a Director (as the position was known in that day), Vice-president in 1879, and President in 1896 until 1907. He resigned because of poor health and only three months later, on March 18, 1907, he died at the age of 68 years.

Mr. Wallach was a commanding figure with a fine face, and a friendly voice, affable to everybody, everyone's friend and advisor, always ready to receive one at his office or at home. His wife always complained that she was "jealous of Lexington Avenue." He was equally friendly in his relations with his associates on the Board of Directors and the Medical Board, and as a result there was complete cooperation, contributing greatly to the welfare of the institution.

The foregoing is but a bare outline of Wallach's life. But those thirty years played a very important part in the development of The Mount Sinai Hospital which had grown from the relatively small institution on Lexington Avenue to the imposing hospital on Fifth Avenue.

The chronology of the many changes may be found in the historical notes in the Annual Report of 1941, "the 90th Anniversary Year, 1852-1942" and also in the recent historical exhibit. One may hope that the many activities under Mr.

Wallach's administration or under his guidance will be detailed more fully in future installments of "The Story of The Mount Sinai Hospital" appearing in the *Journal of The Mount Sinai Hospital*, which is so ably edited by Dr. Joseph H. Globus.

But I shall dwell especially on Mr. Wallach's interest in science and medical education which he evinced for so many years.

His annual messages had many references to his favorite topic. One special plea was made in 1906 and may be found in his splendid style in the epigrammatic phrase "Emblematical of its threefold mission, may its banner with the motto, 'Benevolence, Science, Education', wave over Mount Sinai for all time to come." (Annual Report, p. 49, 1906). An even more eloquent plea may be found in his annual message of 1897 (Annual Report, p. 29-30), and must be quoted in full: "To afford proper accommodation for pathological and microscopic research with a well-equipped laboratory is as necessary now in hospital service as the operating room for the Surgical Department. It is indeed regrettable that for the lack of room these requirements cannot be sufficiently provided to enable our hospital to keep in line with modern scientific demands.

"Benevolence furnishes the means, and science the methods, for the relief of suffering mankind. They stand for the head and heart, for thought and feeling; the one without the aid of the other is without avail; united they cope against disease with force and good results. Stimulated by these two factors, hospitals and charitable institutions are established where both benevolent and scientific work have their place and sphere. Science has, therefore, a just claim upon the funds furnished by the benevolent for the needed facilities and appliances for investigation and research, not only into the many recognized medical developments of this scientific age, but also for the discovery of much that is yet hidden and unknown in this vast region for study. The hospital is the fruitful field for such researches and tests. Every true discovery for the diagnosing and treatment of disease means not only the saving of life for its patients, but for the entire human race. To provide proper accommodations and equipment, and better enable those in the charge of this Institution to carry out its benevolent and scientific objects, we appeal to many in our community who, though able, do not contribute to nor share in this inspiring work. Let those who have not yet joined us visit the wards of our Hospital and see for themselves what is being done. It will engender the feeling that they, too, should bring their offering upon this altar dedicated to humanity—for what greater satisfaction than to have aided in a cause which serves God and man, one which is sustained by the teachings of all religious and social laws?"

Soon after the opening of the new buildings Mr. Wallach had planned a formal inauguration of them with the wide participation of the medical profession. He invited Sir William Osler in the hope that he would make the main address. Osler replied that he would be glad to come to this city to further medical education. How Osler found time one may infer from what Harvey Cushing so graphically described as "that hectic year of 1904 before his going to Oxford?"

Those of us present that evening will recall the outstanding meeting with Osler and Wallach. Recently, Howard Lilienthal and I discussed that meeting and we agreed about the splendid speech of Mr. Wallach who made a deep impression upon the audience. Dr. Lilienthal recalled that "he spoke on architecture, finance, and especially on Education." Osler's address was a most interesting discussion on the relations of the hospital and the clinic in medical education.

There was another side of Isaac Wallach in his relations as a humanitarian. An unusual example of many years ago may now be told by me as a survivor and one of those concerned in the affair in which Mr. Wallach broke one of the most rigid rules of the hospital. The results of his action proved most satisfactory to everyone; the community benefited by more liberal regulations of the Board of Health and by the establishment of the new Minturn Hospital for the private care of patients with contagious diseases.

For many years the Board of Health's rules for contagious diseases in hotels had been very cruel for the patients and their relatives, especially for those exposed to scarlet fever. It was imperative, according to the rules, that such victims be removed to North Brother Island, since at that time the city had no other isolation hospital.

The newspapers of about fifty years ago were full of the details of the story about the well known surgeon, Dr. William T. Bull and Mrs. James Blaine, Jr., the widow of the son of the national political figure, Senator Blaine, who had almost lost the Presidential election for Grover Cleveland. Mrs. Blaine and her child had been living in a hotel which was about to be torn down for a new building when the child contracted scarlet fever. In accordance with the rules, the Board of Health ordered the transfer of the child to North Brother Island, but Dr. Bull insisted upon the right of Mrs. Blaine to have a full quarantine in the deserted hotel and he won a long fight for the mother and the child. At the same time the prize bachelor surgeon succumbed to the charms of the widow and they were married soon afterward.

One early morning, during the same period, Mr. Wallach telephoned me to come to his home on an important matter which could not be discussed on the telephone. When I arrived at his home he informed me most confidentially that Edward Lauterbach, the well known lawyer who had been a director of the hospital and had cared for its legal affairs for many years, had communicated with him with regard to an important client of Mr. Lauterbach, a Mrs. Minturn, who was living in a very well known hotel where her child had been stricken with scarlet fever. The Board of Health demanded the transfer of the child to North Brother Island. The problem presented to Mr. Wallach concerned the rigid rule forbidding admission to the hospital of all persons with contagious disease; and if by some chance a patient already in the hospital became afflicted by a contagious disease he was to be quarantined in a small building in the hospital yard. Mr. Wallach decided that Mrs. Minturn and her child should be assisted in her difficult situation and he asked me to take care of the case. The child was transferred at night from the hotel to the quarantine building in the hospital yard. All the doctors and nurses concerned never revealed the secret. Mrs. Minturn's

deep gratitude and thanks to Mr. Wallach were evidenced soon afterward when she bought land on East 16th Street to establish a private hospital for contagious diseases. The building was erected in 1896 and became known as the Minturn Hospital, which later, in 1928, incorporated with the Willard Parker Hospital.

An exceedingly important chapter in the history of The Mount Sinai Hospital is little known. It recalls the vital changes made in the original plans for the then developing institution and well reflects the wisdom of President Wallach and his associates. While the new building was being erected a great financial disaster occurred as the result of one of the most unfortunate combinations of circumstances in financial history when Morgan in 1901 formed the United States Steel Company which paid untold millions to Carnegie, Schwab, and their Pittsburgh partners. Old New Yorkers may recall the invasion of the thirty-two overnight millionaires who like a swarm of locusts bought everything, especially the favorite real estate on Fifth Avenue for their palaces. Reminders of this epoch are the chateaus of Carnegie, Frick and Schwab. The disastrous result was that all prices climbed skyward. Shortly thereafter the well known North Pacific panic occurred, followed by another crisis a year later which upset everything, especially steel and building materials. The builders were unable to live up to their contracts and unless aided they failed.

Over two million dollars had already been collected for the new buildings, a very large sum even for those days, and the Jewish community was unable to respond further to the frantic appeals by the hospital authorities. The situation was partially hidden in the hospital's Annual Report of 1901, by the short laconic statement: "The loss of funds and the shortage of supplies have changed the plans of the new buildings and everything has been cut to the bone." Thus, great changes in the plans became necessary and resulted in the loss of the projected sixth floor for all the buildings on 100th Street and in the complete upset of almost all the floor plans.

It is hard to believe today how well the ideas for the original buildings were conceived by the Board of Directors and the Medical Board, as represented in the prize plans of Arnold Brunner. The medical and surgical buildings had six floors. The first floor had space for administration and mixed rooms; the next four floors were to be used for two male and two female wards, while the sixth floor was to be divided for the special departments of neurology, gynecology, genito-urinary, dermatology, eye, ear, nose and throat services. The administration building also was to have a sixth floor to provide additional single rooms for the house staff and employees.

What one must emphasize is the master floor plan for the medical and surgical services; they were perfect in every detail. The large wards were planned as they are now, but what was considered new at that time was a special examining room with a large window and good light at the end of each floor; a laboratory for each floor and special rooms for very sick patients. There even was a large closet in the medical building for a portable tub which was utilized in those days for hydrotherapy for patients with typhoid fever. In the same medical building

on the basement floor was a hydrotherapy department with provisions for baths, massage and electric treatments. This space was used later for the enlarged quarters of the x-ray department.

The serious changes caused by the curtailed plans were felt by all the specialties due to the loss of the two sixth floors. Some of the departments were reduced to small wards; some to a few beds scattered in the large wards, while the others were limited to the visits of consultants! The administration building had fared best of all since it had lost only its top floor, crowding the house staff and the employees into smaller quarters.

A sixth floor has recently been erected on the Administration Building affording additional space which has been so badly needed. If only those sixth floors of the original Brunner plans could have been used to round out those brilliant ideas of over fifty years ago!

These pages may remind the present generation of how much is due to Isaac Wallach and to those many years during which he guided The Mount Sinai Hospital, thus contributing so much to its present high status.

# THE ELECTROCARDIOGRAM IN UNCOMPLICATED DISEASE OF THE GALL BLADDER AND THE CHANGES INDUCED BY OPERATION

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That affections of the gall bladder and coronary artery disease are frequently associated is a well attested observation. Thus Schwarz and Herman (1) in a study based on 109 cases found 63.3 per cent associated with myocardial disease, of which 56.5 per cent were combined with obesity. Walsh, Bland, Taquini and White (2) in a study of 2,737 post-mortem observations found that gall bladder disease occurred twice as often in patients with coronary artery disease as in those with normal coronary arteries. They hold that some factor or factors related in part at least to the ageing process is apparently responsible for this association. Breyfogle (3) in a statistical study of 1,493 autopsy records, found that there was a striking and positive association regardless of age and sex between gall bladder disease and coronary artery disease where the latter is the direct or contributing factor toward death. Of a total of 363 cases with gall bladder disease, coronary disease was associated in 79. Tennant and Zimmerman (4) in a series of 1,600 autopsies showed that there is a significant association between the occurrence of heart disease in general and gall bladder disease. However, they also showed by biometric studies that there apparently is no significant association between the two lesions in an age period in which most of the instances of each lie. We are in accord with this view and for the added reason that overweight and its frequent concomitant, hypertension, tend to equalize the incidence of the association.

Of greater clinical significance is the simulation of pain of coronary disease by an attack of cholelithiasis with or without cholecystitis. In such instances, electrocardiographic interpretation is of decisive moment. Unfortunately, such an interpretation is sometimes equivocal so that doubt arises as to whether the patient is afflicted with one or both maladies or both simultaneously. The reason for this lies in the fact that numerous observers report changes in the electrocardiogram arising from uncomplicated disease of the gall bladder, as proven by the disappearance of these changes after operation. Thus Strauss and Hamburger (5) report three cases of ventricular extrasystoles which disappeared within an hour or two, four days and one week respectively after operation. Fitzhugh and Wolferth (6) report in detail three cases:

*Case 1.* A woman, aged 60, complained of severe precordial pain radiating to the left shoulder, usually nocturnal, rarely induced by exertion. These symptoms were present intermittently for many years. The electrocardiogram showed frequent extrasystoles, a tendency to left axis deviation and the T waves were inverted in all three leads. These changes were regarded as evidence of severe myocardial disease. X-ray showed a non-visualizing gall bladder. Six weeks after operation, the T waves were upright in leads I and II and of normal amplitude. Four years later, the patient is well and leads a normal life.

*Case 2.* A woman, aged 38, some years previously suffered severe precordial pains with fainting. Shortly after she had another attack, was then well except for vague precordial pain and left upper quadrant discomfort. Two weeks before consulting her physician, she suffered severe pain in the left upper quadrant with precordial pain radiating to the left arm. X-ray examination showed a poorly functioning gall bladder with calculi. The electrocardiogram showed the T wave practically flat in lead I and inverted in leads II and III, and a diagnosis of myocardial damage was made. Cholecystectomy was performed. Three months later the electrocardiogram was normal.

*Case 3.* A woman, aged 47, had symptoms of gall bladder disease with attacks of pain in the right upper quadrant. For the past two years she suffered severe precordial pain associated with flatulence, most distressing at night and not induced by exercise. The electrocardiogram showed a left ventricular preponderance and inversion of the T waves in leads II and III. A diagnosis of myocardial damage was made. Cholecystectomy was performed. The electrocardiogram eight months later showed the T waves upright in lead II with normal amplitude.

These authors observed three other cases, not reported in detail, in which the electrocardiogram showed deviations from the normal, mostly inverted T waves, and in which operation completely restored the curves to normal. They believe that gall bladder disease may cause a myocardial damage which is reversible.

Boas and Levy (7) report the case of a man, aged 41 years, who in 1932 presented a history of precordial pain on walking. The electrocardiogram was normal. In 1937 he suffered severe abdominal cramps with sharp precordial pain and vomiting, followed on the third day by icterus. The electrocardiogram showed the T waves practically flat in all three leads. Operation revealed a cholecystitis with gravel in the common duct. Six weeks later the electrocardiogram was normal and the patient was free from symptoms.

Weiss and Hamilton (8) studied the electrocardiogram of 21 patients with chronic cholecystitis with cholelithiasis who underwent surgery. In none were chest pains significant of angina pectoris present. A significant electrocardiogram was found in four cases, as evidenced by inverted T waves and in one patient depression of the ST interval in lead II. In three, the electrocardiogram returned to normal after operation; in the fourth the patient had hypertensive disease.

Willius and Fitzpatrick (9) in discussing the relationship of chronic infection of the gall bladder to disease of the cardiovascular system report numerous instances of electrocardiographic changes in 34 per cent of their cases; auricular fibrillation, T wave negativity, delayed AV conduction (2 cases), aberration of the QRS complexes and premature contractions.

Buchbinder (10) in a measure confirmed these clinical observations experimentally. After ligation and division of the common bile duct in puppies, the most frequent abnormality is inversion of the T wave. Of nine instances in which jaundice was produced, six developed negativity of the T wave. In two, the T wave was inverted in all leads, in another, negativity occurred in leads II and III, and in two others in leads I and III. These changes developed between the third and sixty-fifth day. The negativity was transient in most instances and was permanent in only a few. In no case, was there observed a prolonged

PR interval or an aberrant QRS complex. He regards the mechanical factor produced by distension of the intra- and extrahepatic ducts as a cause of disturbed rhythms accompanying certain cases of cholecystitis without frank jaundice.

The following case is reported not merely to corroborate the thesis of this paper, but more especially to record an instance of an unusual change in the electrocardiogram that has been reported by only one previous set of observers (Willius and Fitzpatrick).

#### CASE REPORT

*History.* A man, aged 44 years, who had hitherto been in good health except for an attack of nephrolithiasis with the passage of a uric acid stone some two years previously, was suddenly seized with a severe precordial pain, non-radiating, accompanied by nausea and vomiting. The pain subsided promptly after a hypodermic injection of morphine sulfate gr.  $\frac{1}{4}$  and he was admitted to The Mount Sinai Hospital for observation.

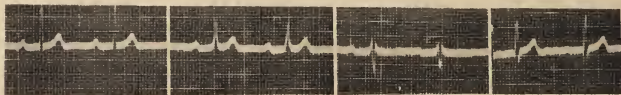


FIG. 1. Preoperative electrocardiogram showing prolonged PR interval (period .30 second).

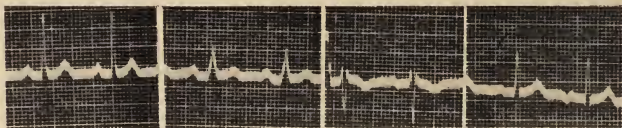


FIG. 2. Electrocardiogram taken sixteen days after operation showing normal electrocardiogram except for left ventricular preponderance. PR interval now .16 to .20 second.

*Examination:* There was no rise in temperature and the leucocyte and differential count was perfectly normal. The heart sounds were regular, rate 64, no murmurs; the epigastrium was not tender. The electrocardiogram (fig. 1) in addition to a left ventricular preponderance showed a distinctly prolonged PR interval (.30 sec.) and in view of the precordial pain, a diagnosis of coronary disease was considered. However, a gall bladder x-ray taken two days later showed non-visualization.

*Course:* Cholecystectomy performed by Dr. Ralph Colp revealed four fairly large faceted calculi. Convalescence was uneventful. An electrocardiogram (fig. 2) taken 16 days after operation showed a normal PR interval. The patient has been well since.

#### COMMENT

It is evident that uncomplicated disease of the gall bladder may affect the electrocardiographic curve, the predominant change being flattening or inversion of the T waves in two or more leads. The precise mechanism is, in the light of our present knowledge, entirely hypothetical. It is plausible to think that there is latent myocardial dysfunction due to coronary sclerosis which renders the

electrocardiographic curve more susceptible to changes consequent upon the trauma of the superimposed malady within the gall bladder. This can only be determined with certainty by a follow-up of a large series of such recorded cases. However, the fact that the age of some of the patients is lower than that in which clinical coronary disease usually arises argues against this possibility.

#### CONCLUSIONS

Uncomplicated gall bladder disease may affect the electrocardiographic curve, as proven by its restoration to normal after operation. In the majority of instances the changes represent flattening or inversion of the T waves, less frequently extrasystoles.

A case is reported, the third on record, in which the change was represented by a prolonged PR interval. The mechanism whereby these changes occur is not clear.

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## THE EVOLUTION OF THE TREATMENT OF PULMONARY TUBERCULOSIS BY MECHANICAL (SURGICAL) MEASURES

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It is fitting that a survey of the evolution of mechanical measures devised to control pulmonary tuberculosis should be included in a volume dedicated to Alfred Meyer, an American pioneer in treatment by pneumothorax. Collapse therapy by pneumothorax not only was the initial method boldly conceived by Forlanini but also remains the procedure by which the greatest number of curative results can be and are achieved. This is all the more remarkable in view of the many other surgical measures which have been advocated and employed. Indeed one may say that there would be scarcely any place for other mechanical measures in the treatment of pulmonary tuberculosis were pneumothorax therapy initiated in good time in the great preponderance of cases. To state it in another way it can be said that the development of other surgical measures which are for the most part less effective and surely more dangerous and mutilating really has taken place because pneumothorax either has been omitted or has been begun too late. Pneumothorax remains the sovereign remedy.

The pioneers had a clear idea of the purpose of pneumothorax which was and is to collapse the tuberculous cavity. Following them, however, a school of thought arose which maintained that the objective of mechanical measures of any sort was a form of rest applied to the affected lung as well as a change in the circulation of blood and lymph resulting from the relaxation of the lung. This thought led to the development of two methods of surgical treatment, phrenicectomy and paravertebral thoracoplasty, which now will be briefly discussed.

Concerning phrenicectomy, a measure of rest and relaxation of the upper lobe was thought to be achieved by the elimination of the rhythmic pumping action of the diaphragm. The theory was that the healing of cavities in the upper lobe was thereby invited. In the case of cavities in the lower lobe the direct compression produced by the elevation of the diaphragm was believed to be the effective factor. Usually phrenicectomy was employed after pneumothorax had been attempted and had failed but there were some who advocated phrenicectomy as a better method than pneumothorax under specified circumstances. In any event phrenicectomy has been practised in many thousands of cases. A vast literature has come in its wake. Such a literature, by the way largely contributed by proponents of the method, renders bold a categorical statement to the effect that the method is of little value. It appears safe to say, however, that phrenicectomy can be proven to result in the collapse of cavities only in rare instances, and thus at best should be regarded today as worthy of trial only in carefully selected cases.

Passing reference can be made to a feature of the technique of phrenicectomy which is undesirable. First it should be said that there was early recognition of the fact that the accessory phrenic nerve as well as the main trunk would require

severance in order to produce complete paralysis of the diaphragm. Because the objective was a prolonged paralysis of the diaphragm and because the accessory phrenic nerve, situated behind the parent trunk in the neck, joined the main nerve at a variable point and often within the thorax, there was evolved an operation which consisted of avulsion of the main trunk in the neck. This violently traumatic procedure was of course effective since the accessory as well as the main trunk were detached but it left in its wake permanent paralysis of the diaphragm. It came to be realized that a lasting paralysis of the diaphragm could, for a variety of reasons, prove to be a most undesirable condition. It can be said at the present time that a satisfactory procedure should consist of a phrenic operation which would paralyze the diaphragm for about six months. From three to eight months or more of paralysis of the diaphragm can be obtained in a precise surgical manner by dissection of the main and accessory phrenics in the neck followed by the severance of the accessory nerve and then the severance and approximation by suture of the main trunk. There is no longer any justification for the operation of avulsion of the phrenic nerve.

Paravertebral thoracoplasty is the procedure with which Sauerbruch's name is commonly associated. The operation consisted of excision of small segments of the ribs in the paravertebral region with the object, as stated, of achieving rest of, and altered circulation in, the lung. It is of interest to note that this operative procedure soon superceded that of widespread removal of the upper ribs which had been originally advocated for the purpose of producing collapse of cavities but was found to be too dangerous. Good results were reported by Sauerbruch and by others and the operation therefore was very generally practised throughout the world. Only tardily was it learned that the "good results" consisted largely of "improvement" or "ability to return to work" and only rarely of the collapse of cavities and the disappearance of tubercle bacilli from the sputum. Untold thousands of patients have been subjected to paravertebral thoracoplasty but collapse of cavities can have resulted only rarely because the operation was, mechanically speaking, defective.

The wave of reaction against the poor results of paravertebral thoracoplasty led to selective upper thoracoplasty in which long segments of the upper ribs were removed in order to achieve collapse of cavities. Essentially this was a reversion to the operation which had been originally advocated. Genuine collapse of cavities was now obtainable and a great enthusiasm for the operation naturally was engendered. Unfortunately, rather indiscriminating or uncritical reports of excellent results in great numbers made their appearance in the literature. There resulted a period in which there was an assumption that a sufficiently extensive decostaliation would, generally speaking, lead to good results in the true sense of the term (collapse of cavities). When for example as recently as 1933 I presented an argument in favor of a direct release of stiff-walled cavities by an advocated procedure which I termed cavernolysis, the rebuttal by surgeons of large experience was that cure could be achieved without resort to such measures provided long enough segments of ribs were removed. Collapse of cavities was achieved unquestionably in a substantial proportion of cases

but there was lacking a critical analysis of results. I was perhaps the first to demonstrate in a large series of cases the value of bronchography in disclosing the results of thoracoplastic procedures. It demonstrated all too often the persistence of a cavity or cavities which could not be identified in ordinary roentgen films. Subsequently sectional radiography proved to be extremely useful in revealing the persistence after thoracoplasty of perhaps unsuspected cavities.

The realization that not infrequently cavities remain uncollapsed by thoracoplasty no matter how extensive the rib resection led to the addition of release of the cavity-bearing portion of the lung in selected cases. Of the various procedures which have been advocated for the purpose that devised by Semb has been most widely employed. It consists of a liberal release of much of the upper lobe so that the diseased portion of the lung can descend vertically in the thorax. Thus the collapse which may be achieved will be from above downwards and not towards the vertebral column as after thoracoplasty without release of the lung. Under the latter circumstances cavities often were held partly open because the apex of the lung, not being released, remained a point of attachment from which the cavity hung. This of course was impossible when the apex was released. Accordingly a higher incidence of collapsed cavities could be anticipated with the Semb technique and this in fact proved to be true. However, a substantial proportion of failures was inevitable since a cavity may drop a considerable distance but its collapse depends on the intrinsic pull within the lung. In the absence of much elastic recoil the cavity may be but little affected even after wide release of the upper lobe. In order to aid and maintain collapse I (like others I am sure) have manually compressed the cavity by external pressure at the time of release of the upper lobe and have attempted to maintain collapse by placing a purse string suture through thickened pleura (and probably underlying lung) around the depressed area. This has been successful in a number of cases but collapse might possibly have been achieved in these cases without this additional step.

A direct method for obtaining collapse of cavities has been the intrapleural division of adhesions or bands suspending cavities from the superior aperture of the thorax. Excellent results have been achieved at times when the severance of such adhesions existing in the form of bands or strings has resulted in release of the cavity-bearing portion of the lung. Occasionally widespread dissection of a more broadly adherent upper lobe also has given results although under such circumstances the incidents of good results has been lowered and the dangers of the operation have increased. There have also been instances in which complete release of the cavity has not resulted in collapse of the cavity because of the lack of intrinsic elastic recoil. The evidence is clear that in well selected cases, intrapleural pneumonolysis is an excellent procedure which can well be regarded as of decisive assistance to pneumothorax.

It would go too far afield to discuss or analyse in this place the relative merits of the procedures which have been touched upon in this brief survey of the mechanical measures that have been employed to collapse cavities. Not all methods have been mentioned yet it is evident from the foregoing that the search for a

method which would offer uniformly good results is not over. At long last it is recognized today that not all cavities are collapsible and that therefore it is illogical to attempt collapse of certain stiff-walled cavities by thoracoplasty either with or without release of the lung. This belated recognition has led on the one hand to drainage methods, and on the other hand to removal of the affected lobe or lung. It is as yet too early to attempt an evaluation of these procedures which are in a direction diametrically opposite to thoracoplasty. They do point, however, to a realization that there are limitations to the efficacy of thoracoplasty which now is known to have its great disappointments as well as its brilliant results. Indeed it can be said that in any given case the outcome of thoracoplasty is uncertain because in the last analysis collapse of the cavity depends directly on the intrinsic elastic recoil of the lung around the cavity and only indirectly on the operation. This uncertainty must of necessity place thoracoplasty among operations whose results are not predictable.

This survey of the evolution of thoracoplasty apparently points to the limitations of what can be done by surgery for a bad situation. For the bad situation is any case in which thoracoplasty must be considered and practised. Most patients should not reach that stage. If cases of abscess of the lung are properly cared for in the acute stage the far more difficult problem of chronic abscess of the lung will not exist. If pulmonary tuberculosis is properly cared for at an early stage, chiefly by pneumothorax therapy, the bad situation requiring thoracoplasty or other major procedures will rarely be required. This fact only throws into bolder relief the picture of the great contribution made by the pioneers of pneumothorax therapy. At the present time surgeons as well as internists should gladly advocate a more general application of early pneumothorax therapy and thereby virtually eliminate thoracoplasty or other major surgical procedures for the collapse of pulmonary cavities.

# SIMMONDS' DISEASE VERSUS ANOREXIA NERVOSA

## A REPORT OF A CASE WITH NECROPSY FINDINGS

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In 1868 Dr. William W. Gull (1) delivered the Address in Medicine at Oxford before the British Medical Association. Buried in this lecture is the following sentence which is the first printed reference which Gull made to a condition which he subsequently called *anorexia nervosa*, and upon which his claim to being the first to describe this condition rests. "At present our diagnosis is mostly one of inference, from our knowledge of the liability of the several organs to particular lesions; thus we avoid the error of supposing the presence of mesenteric disease in young women emaciated to the last degree through hysteric apepsia, by our knowledge of the latter affection, and by the absence of tubercular disease elsewhere." It was not until 1874 that he published his classic paper on *Anorexia Nervosa* (*Apepsia Hysterica*, *Anorexia Hysterica*) in the *Clinical Society's Transactions* (2) describing in detail three typical cases with facsimiles of the original photographs of the patients exhibited at the time the paper was read. He referred to the "peculiar form of disease occurring mostly in young women, and characterized by extreme emaciation, and often referred to latent tubercle and mesenterics disease." He observed that no determining cause for this affection was known. He also noted that the victims of this deformity were mostly of the female sex, chiefly between the ages of 16 and 23, although occasionally he had seen the same cachectic condition in males of the same age. It appears that while Gull was writing this paper in 1874 his attention was called by a friend to a paper by Dr. Lasègue (3) of Paris which had appeared in 1873, and he observes that it is plain that both he and Lasègue had the same malady in mind. Gull says very properly that it is most unlikely that Lasègue knew anything of his original communication in the *Lancet*, and it is quite clear even today that anyone who seeks the original reference must hunt very carefully through the address delivered at Oxford to find mention of *apepsia hysterica*, the term which Gull originally used. Gull subsequently employed the term *anorexia nervosa*, and Lasègue the name *anorexie hystérique*. Lasègue undoubtedly was describing the identical condition, as he mentions the cachexia, amenorrhea, scaphoid abdomen, the progressive diminution of the elasticity of the abdominal wall, epigastric tenderness, obstinate constipation, the dry rugous inelastic skin, the tendency to vertigo, to attacks of syncope, etc. Lasègue shows a remarkable psychologic insight into the psyche of these patients and one which would probably be approved of by contemporary psycho-analysts. It is extraordinarily interesting to see the difference in description of the same condition by a British and by a French internist. Gull too believed the lack of appetite to be due to a "morbid mental state", and stated that "young women at the ages named are especially obnoxious to mental perversity."

In the course of his clinical descriptions Gull speaks of some peevishness of

temper, a peculiar restlessness which is difficult to control, a persistent wish on the part of the patient to be on the move, and the fact that the mother of one of his three patients subsequently added that "she is never tired". He also observed that when the emaciation of such patients is at the extreme, edema may supervene in the lower extremities. Altogether the original descriptions of both Gull and Lasègue make most interesting reading even at the present time.

In 1914 Morris Simmonds (4), pathologist to the University of Hamburg, announced his discovery that cachexia was associated with destruction of the adenohypophysis. He amplified these observations in subsequent papers, and by 1922 his fellow townsman, Prof. Lichtwitz, called the condition Simmonds' disease. In 1930 Philip E. Smith (5) succeeded in aspirating the rat's hypophysis without injury to adjoining portions of the brain, and thereby produced experimentally what may be called the same disease in rats. He also showed that the hormonal deficiency can be relieved by implanting the pituitary gland. There was, therefore, the pathologic evidence of the destruction of the adenohypophysis with the clinical picture in man, and the confirmation by Smith's remarkable experimental work in removing the anterior lobe of the pituitary gland and then relieving the consequent disorder by substitution therapy.

In 1931 Farquharson and Duncan Graham (6) reported three cases of Simmonds' disease with the findings of the post-mortem examination in one of these before the Association of American Physicians. In the course of the discussion Oppenheimer (7) stated that this was the first instance of Simmonds' disease to be published in America with a report of the pathologic findings of the pituitary gland. In addition he stated, "In 1929 a case of Simmonds' disease was observed by Dr. S. Silver (8) on my service, and will be published by him. This case was diagnosed during life, and necropsy disclosed advanced lesions in the anterior lobe of the pituitary as the only significant pathological finding. The anterior lobe showed marked degeneration and atrophy of its cells. The etiology of the destructive process was not determined. Another patient, whom I still have under observation after twenty-three years, has the clinical characteristics of Simmonds' disease, and the diagnosis has been confirmed by Lichtwitz and H. Zondek, who have had special experience in this disease. The symptoms followed her first and only pregnancy, at which time she showed the characteristic premature ageing and most of the other findings which have been reviewed by Dr. Graham. The depression of the basal metabolic rate was extreme, reaching minus 46 per cent and even lower, with normal respiratory quotients. Reye pointed out that there are these prolonged cases of Simmonds' disease which may last for many years. Reiche reported a case, confirmed by post-mortem examination of the pituitary gland, which lived for forty-four years after the onset of symptoms. There can be little doubt that similar cases of hypophyseal cachexia are being missed in America because attention has not been sufficiently directed to the disease. This may be due to the fact that Simmonds' original publication appeared in 1914, at the time of the outbreak of the war. In any case of unexplained emaciation or cachexia, Simmonds' disease should at least be considered, and if opportunity is afforded the anterior lobe of the pituitary

should be examined for pathologic lesions." No further reference to the above-mentioned case was made in the literature until the publication by Escamilla and Lisser (9).

Finally in 1943 Escamilla and Lisser published a most comprehensive review of Simmonds' disease, reporting every possible case in the literature and including a group of cases of anorexia nervosa for purposes of comparison. Everyone working in this field will feel deeply indebted to these authors for their admirable review of the subject of hypophyseal cachexia and of anorexia nervosa, and the present author feels grateful to them for their footnote 8 in which they state, "We have been unable to find any record of this case except in Oppenheimer's discussion of the paper of Farquharson and Graham." In their doubt, therefore, they thought the case belonged to what they have designated as group B which consists of typical clinical cases of Simmonds' disease without pathological investigation. It is this note by Escamilla and Lisser which was the motive which led to the present republication of the case which is reported in the following notes. It may be stated at once that this particular patient, after suffering for some twenty-eight years from anorexia, finally died of a perforated carcinoma of the esophagus, and that a careful gross and histologic examination of the pituitary gland revealed no significant abnormalities. Therefore, this case should properly be assigned, in the classification of Escamilla and Lisser, to group F which comprises typical clinical cases of Simmonds' disease, but with normal pituitaries. It should be added that Escamilla and Lisser have quoted from the literature fourteen other cases in this category F, but they say that six of these showed definite gross pathology in close proximity to the anterior lobe of the pituitary. "Since all of these cases were typical clinically of Simmonds' disease, interference with the function of the adeno-hypophysis is conceivable although no cellular changes were found. Such a supposition seems tenable when one reflects on the intimate neural connections which link the hypophysis and hypothalamus (9)."

The following, therefore, is a summary of the case which was briefly referred to in the discussion of Farquharson and Graham's report of 1931, and in the footnote of Escamilla and Lisser's comprehensive survey. The clinical history may now be completed with a report of the autopsy performed in 1936. Whether or not this case should be called Simmonds' disease, pseudo-Simmonds' disease, or anorexia nervosa is an open question.

#### CASE REPORT

*History:* (Adm. 394783; P. M. 9965). A woman, aged 61 years, entered the hospital on June 19, 1936. Her mother had always been stout; a chronic invalid with a dominant personality who suffered from essential hypertension and died of acute cerebral apoplexy. Her father died of heart disease at the age of 70 while golfing.

The patient was fairly plump until the onset of her illness. At the age of 29 she came under the care of Prof. Friedrich Mueller of Munich for a so-called gastric ulcer. Subsequently she married and in 1908 she gave birth to her first and only child. It was during the puerperal period that she began to display the first definite symptoms of her fatal illness. After giving birth to a healthy child, she was very resistant to getting out of bed, refused to eat, and thereafter became gradually more emaciated so that her average weight

in 1927 was about 76 pounds and dropped to 59½ on her admission to The Mount Sinai Hospital. She had amenorrhea since the first pregnancy. The father always ascribed her refusal to eat to the fact that she was apprehensive of getting as fat as her mother had been. Since 1908 she had been very thin, had had a mucus colic, which was very troublesome, and for which she demanded frequent colonic irrigations. She was on an extremely limited diet. She was constipated, usually spending an hour or more at every stool. She complained of rheumatic pains in various joints. With the visceroptosis she also developed a prolapse of the rectum which was operated upon by Dr. William Mayo in 1920. In 1921 she had an acute pyelitis with fever and a prolapse of the urethral mucous membrane which required operation by Dr. Hiram N. Vineberg, the gynecologist. Hemorrhoids and mild bleeding troubled her from time to time. For several years she had a persistent cough which was treated, but no evidence of tuberculosis could be found in x-ray films of her chest or in the sputum.

On March 7, 1922 she entered the Montefiore Hospital. On March 21 she fainted in the tub and suffered a contusion of the skull. Her weight was about 66 pounds. A basal metabolic rate on April 4 was minus 35 per cent and minus 30 per cent. While in Montefiore Hospital she was seen by Dr. David Marine who recommended adrenal cortical extract. She gained about 4 pounds, but did not profit otherwise from her stay in that hospital.

In June 1922 she came under the care of an experienced dietitian who found that her intake was at most 900 calories. Her weight, when dressed, was at first 69 pounds and her height was 59¾ inches. On April 20, 1922 her basal metabolic rate was minus 50 per cent and she weighed 71 pounds.

In April 1927 an x-ray examination of the skull was reported by Dr. Bendick as showing no pathologic changes. The sella turcica was small but still within normal limits. At that time the tentative diagnosis was either Simmonds' disease or anorexia nervosa.

In August 1927 she was observed by Prof. Herman Zondek, who made a very detailed study and found the following: lungs, a dull note and increased respiratory murmur on the right side; heart, no abnormalities; x-ray examination of the chest, negative; blood pressure, 90 systolic; pulse rate, 54 per minute; reflexes, no abnormality; urine, negative for albumin and sugar; urobilinogen, not increased; erythrocyte sedimentation rate, normal; blood hemoglobin, 60 per cent; sugar, 88 mg. per cent; red blood cells, 3,000,000; leucocytes, 6,400; sputum, negative for tubercle bacilli; stool, no occult blood, membranous shreds, colitis mucosa; stomach contents, free hydrochloric acid 8, total acidity 12, no blood, no lactic acid, positive for pepsin; x-ray examination of the stomach, marked gastropexia with normal emptying time, normal contour, normal pyloric function. Gas metabolism, according to Knipping: Oxygen requirement 177.5 cc. per minute; per kg. 5.2. Carbon dioxide excretion 187.2 cc. per minute; per kg. 4.09. Respiratory quotient 0.7, weight 33½ kg.

The patient was put on a constant diet and 10 grams sodium chloride were added. She excreted only 2 grams of this additional 10 grams of sodium chloride (retention of sodium chloride). Water test according to Volhard: after the administration of 1000 cc. of fluid, in 4 hours only 575 cc. were excreted (oliguria). In Dr. Zondek's opinion the diminished excretion of sodium chloride and water indicated the probable diagnosis of a functional disturbance in the region of the hypophysis, although osmo-regulatory disturbances of a marked grade were not demonstrable in the blood. He believed therefore that Dr. Oppenheimer's suspicion that there was a hypophyseal cachexia was correct. In any event, Dr. Zondek considered the condition a benign form of hypophyseal cachexia of which he had seen many cases which improved and the patients continued to live for many years. Therapeutically he recommended a cautious attempt at "insulin cure." This was administered in doses of 4-6 units of insulin but even this small dose was followed by mild hypoglycemic symptoms. In addition he recommended small doses of thyroindine. He also gave the patient calcium and hypophyseal tablets as well as an appropriate diet. On two occasions Dr. Lichtwitz saw the patient and also thought the case was one of Simmonds' disease.

On October 30, 1928 the patient's weight was 77 pounds. She was then put on praeparation parenterally but, as it caused a chill and rise of temperature, it was stopped. The symp-

toms continued and about December 1935 she also began to complain of mild pains across the lower chest. X-ray examination disclosed a tent-like adhesion on the pleural surface of both diaphragmatic leaves. The pain subsided but returned in March 1936. Three weeks before admission to The Mount Sinai Hospital she refused food because eating increased the severity of the pain. At the same time small doses of thyroid extract (1 grain, three times a day) were taken by her for 4 or 5 days. As she failed to improve, it was decided to have her enter the hospital in order to carry out duodenal feedings; however, she refused to cooperate in the procedure. On June 16, 1936 complete gastro-intestinal x-ray examination revealed no lesion except a ptosis of the organs. (Unfortunately the lesion in the esophagus was not discovered).

*Examination.* The patient was markedly cachectic and pale. Her skin was dry, wrinkled, and inelastic. The scalp hair was black (not grey), pubic hair was present. There was no dyspnea, no cyanosis or jaundice. The head showed no abnormality. Hearing was good. The pupils were contracted, round, equal, and reacted to light and in accommodation. The conjunctivae were pale, there was no nystagmus, no palsies and no petechiae. The mouth showed no ulcerations. Tonsillar tissue was present. The throat showed no abnormality. There was no thyroid enlargement or lymphadenopathy. The breasts were thin and atrophic. The percussion of the chest was hyperresonant. There were a few dry râles anteriorly near the sternum, otherwise examination of the lungs showed no abnormality. The heart rate was 60 beats per minute; sounds of fair quality; rhythm regular; no murmurs; the second aortic sound and second pulmonic sound were equal. The blood pressure was 108 systolic and 86 diastolic and 98 systolic and 76 diastolic. The abdomen was extremely thin, scaphoid, emaciated. There were prominent dilated superficial veins visible; generalized abdominal tenderness; the liver, spleen and kidneys were not palpable. There were no hernias. The extremities were thin, the muscles atrophic. The dorsalis pedis pulses were readily palpable. There were some ecchymotic areas on the legs.

*Laboratory data.* The blood count on June 19, 1936 was as follows: hemoglobin, 78 per cent; red blood cells, 4,950,000; white blood cells, 14,000 with 70 per cent polymorphonuclear leucocytes; 3 per cent eosinophiles; 2 per cent mononuclear leucocytes; 25 per cent lymphocytes. On June 20 the blood sugar was 45 mg. per cent. The blood pressure was 118 systolic and 90 diastolic. On June 25 the blood sugar was 85 mg. per cent; calcium 9.4 mg. per cent. Examination of the urine revealed no abnormality.

*Course.* During her brief stay in the hospital the patient refused duodenal feeding. She ran an irregular fever with temperature to 101°F. She received two intravenous infusions of 1500 cc. of 5 per cent glucose. Her condition declined rapidly and she died on July 5, 1936.

*Necropsy findings. Gross:* The body is that of an extremely emaciated white female of 61 years, in incomplete rigor mortis. The skin is wrinkled and inelastic and can be picked up in large folds. The skeleton is prominent. There is no jaundice, edema, cyanosis or petechiae. The hair is black. There is a midline, suprapubic, smooth scar extending midway up to the umbilicus.

*Abdominal cavity:* The panniculus adiposus is very thin. There is almost complete disappearance of the subcutaneous and mesenteric fat. There is a generalized visceropotosis. The liver extends 3 fingers below the costal margin. The diaphragmatic dome on the right reaches to the fourth interspace, on the left to the fifth rib. There are adhesions binding the omentum to the anterior abdominal wall and the gall bladder to the small intestine. There is no free fluid in the peritoneal cavity. The peritoneum is smooth and glistening except for the areas of adhesion. The femoral veins milk freely.

*Thorax:* There are bilateral, fibrous adhesions between the lung and lower lateral chest wall. There is no free fluid in the pleural cavities. There are no thymic remains present.

*Esophagus:* The esophagus is cylindrically dilated throughout its course. The middle third of the esophagus shows on its anterior and lateral walls a large, irregularly oval ulcerated, flat, saucer shaped growth, measuring 7 cm. in length and 5 cm. in width. This

growth occupies almost the entire circumference of the esophagus. It is sharply demarcated from the adjacent esophageal mucosa. The edges are heaped up for about 2 mm. The growth consists of an irregularly granular, firm, gray tissue. The center is more scooped out and presents an irregular perforation measuring 2 cm. in length and 1.5 cm. in width, leading into the left main bronchus. The edges of the perforation are ragged and show many small, firm, grayish, papillary projections. These nodules also occupy a small, firm, grayish, narrow 2 cm. zone of the left main bronchus around the perforation. The growth causes no stenosis of the esophageal lumen. In this area the esophagus is adherent to the trachea and bronchi anteriorly and to the arch of the aorta and hila of the lungs laterally by grayish, firm, fibrous tissue which appears much denser than the normal mediastinal tissue. The mucosa of the lower third of the esophagus shows several small, white glistening plaques arranged in the longitudinal axis of the esophagus. There are a small number of peri-esophageal lymph nodes measuring up to 0.5 cm. in diameter. They are soft and show a moist, pinkish gray cut surface. The trachea is grossly normal. The left main bronchus shows a perforation of its posterior wall forming the previously described broncho-esophageal fistula. The perforation extends about 2 cm. down the bronchus from 1 cm. below the bifurcation. It is 0.5 cm. wide. Below this perforation the mucosa of the left main bronchus is thickened, granular and markedly congested.

*Thyroid:* The thyroid is not atrophied or enlarged. It contains no nodules. The cut surface is light brown with the colloid filled follicles showing as yellowish brown pinpoint dots.

*Heart:* The heart is small weighing 150 grams. The pericardial surfaces are smooth and glistening. There is no free fluid in the pericardial cavity. The subepicardial fat is very scant. The myocardium throughout is thin and yellowish brown. The chambers of the heart are not dilated or hypertrophied. The endocardium is thin and smooth throughout. The valve leaflets are all thin and smooth, except for slight thickening along the line of closure of the mitral valve. The chordae tendineae are not thickened and insert in the usual weblike fashion on the mitral and tricuspid valves. There is no fusion or separation of the cusps of the aortic or pulmonic valves. The foramen ovale is closed.

The coronary ostia are patent. The coronary arteries and their main branches are patent throughout. They show scattered subintimal yellowish white plaques which do not narrow the lumen appreciably.

The aorta presents scattered, yellowish, raised, subintimal plaques. The aorta is elastic.

*Lungs:* They are voluminous and keep their shape when placed on the table. They are pinkish gray with a moderate amount of anthracotic mottling. The visceral pleura over both lower lobes shows patches of fibrous thickening. On section the lungs are dark red and ooze a frothy serosanguinous fluid. The parenchyma shows a distinct texture. Scattered through all the lobes, except the right middle lobe, are small irregularly grayish moist areas which are granular and moderately firm. These areas are most prominent at the base of the left lower lobe where they are distinctly raised and in places yellowish. Some of these areas are distinctly confined to lobules surrounding small bronchi and lined by septa. There are some lymph nodes at the hila of the lungs. The cut surface of these nodes is moist and black with a few gray, fibrous strands. The pulmonary vessels show no gross changes.

*Liver:* This organ is small and flat, weighing 850 grams. It is moderately firm. The capsule is thin and the surface is brownish red with mottled yellow areas with several subcapsular, gray fibrous, slightly depressed zones. The cut surface is brown. The architecture is regular with red central areas surrounded by yellowish brown peripheral zones. The hepatic and portal veins are without gross changes.

*Gall bladder:* It is not dilated or thickened. It contains dark brown viscid brown bile. No stones are present. The bile ducts show no gross changes.

*Spleen:* It is normal in size, weighing 95 grams. Its capsule is thin and slightly wrinkled. The cut surface is dark red. The follicles appear as prominent, numerous, gray pinpoints.

The trabeculations are prominent. The cut surface is moist and scrapes blood and a little pulp. The splenic vein and artery show no gross changes.

*Pancreas:* It is normal in size and moderately firm. The cut surface is yellow and lobulated.

*Adrenals:* Normal in size, with the cortex and medulla well demarcated.

*Genito-Urinary Tract:* Kidneys: They are of average size, weighing 210 grams. The surface is red and smooth. The capsule strips easily. The cortex is not diminished in width and the cortical markings are distinct. The glomeruli stand out as red pinpoints. The medulla pelvis, ureters and bladder show no gross changes.

*Uterus:* It is small and firm. The endometrium of the cervix and body is smooth and glistening. There are no nodules present in the myometrium. The serosal surface is smooth. The tubes are patent and not thickened.

*Ovaries:* They are grayish white, small and scarred. The right ovary contains a very small serous cyst.

*Gastro-intestinal Tract:* The esophagus is described above. The stomach shows no gross changes, except for slight congestion. The rugi are well preserved. The small and large intestines show no gross changes. The appendix is not present.

*Bones:* The skull is thin and contains many irregular, dark areas throughout. The bone marrow (lumbar) shows no gross changes.

*Brain* (report by Dr. Joseph H. Globus): The scalp, calvarium and dura are normal. The leptomeninges are not unusual and the vessels show no pathologic changes. The brain is normal in size and consistency and shows mild widening of the sulci, which is entirely compatible with the age of the patient. On sectioning the brain shows no anomalies of significance. The venous sinuses, middle ear, and cranial nerves display no pathologic alterations. There are a few fine adhesions about the pituitary stalk and optic chiasm. Upon close examination the pituitary appears to be normal in all its aspects.

*Microscopic Description. Heart:* Many of the muscle fibers are thinned. Many contain collections of yellowish brown pigment, mainly concentrated on either side of the nuclei. The endocardium, pericardium and vessels are normal.

*Lungs:* There are areas of alveolar distention with breaking down of alveolar walls and coalescence of alveoli. In other regions the alveolar walls are thickened. There are focal areas of atelectasis. In some areas the alveoli are filled with a loose fibrin network, many polys, and some lymphocytes and polys. In other regions the alveoli contain only polys and monocytes, in many others they are filled with edema fluid. One of the large bronchi contains vegetable cells and the walls of the large bronchi show acute inflammation. There are blue staining masses of bacteria in some of the bronchi and alveoli. The hilar lymph node is anthracotic.

*Esophagus:* There is an infiltrating squamous cell carcinoma with numerous pearl formations. The cells are large, irregular, atypical and many are hyperchromatic. There are a number of mitoses. The carcinoma infiltrates into the muscle and there is one small carcinomatous nodule in the perineural lymphatic in the fibrosa. The epithelium over the tumor is ulcerated. The adjoining mucosa shows thickening of the epithelium with occasional mitoses in the basal cells and chronic and acute inflammation with connective-tissue thickening beneath the epithelium. The regional lymph nodes show no metastases. They show numerous polys and some eosinophiles in the sinuses and pulp.

*Liver:* The cells around the central veins are narrowed and contain much yellowish green pigment. The sinusoids are widened and congested. The spaces of Disse are prominent and in some areas contain eosinophilic debris. The liver cell outlines are indistinct. The cytoplasmic structure is blurred. The nuclei are well preserved.

*Spleen:* The pulp is congested. It contains numerous eosinophiles and plasma cells.

*Pancreas:* Negative. The island tissue is abundant.

*Adrenal:* No changes outside of a few round cells in the medulla.

*Kidneys:* There are a few hyalinized glomeruli and thickening of several arterioles.

The tubules contain hyaline casts.

*Ovary:* No ova seen. Several corpora albicantia present.

*Bone* (Skull and vertebrae): bone and bone marrow show no changes.

*Coeliac plexus:* Brown pigment in ganglion cells.

*Brain:* In the hematoxylin and eosin sections, the meninges show a slight amount of fibrous thickening. The larger blood vessels show intimal thickening while the smaller ones show hyalinization with reduction of the lumina. The cerebral cortex shows degeneration of the nerve cells. Some show shrunken darkly staining cytoplasm with pyknotic nuclei while others are markedly swollen with a peripheral ring of dark chromatin granules. A few of the latter cells appear as though without nuclei. The glial elements are more numerous than is usual and in many instances may be seen satellitosis and neuronophagia.

*Diagnosis:* Arteriosclerotic Encephalopathy.

*Pituitary:* In all the subdivisions of the pituitary gland—the anterior lobe, pars intermedia, the posterior lobe—there are no alterations which may be regarded as pathologic. The individual cells show no alterations of any significance. There is no unusual disproportion of eosinophiles or basophiles. The supportive connective tissue is within normal limits, showing no increase.

It may be concluded that the pituitary gland is essentially normal.

*Summary of Anatomical Findings:* Ulcerating carcinoma of esophagus with perforation into left main bronchus. Leukoplakia of the esophagus. Acute hemorrhagic bronchitis, left lung. Bronchopneumonia, left lung, right upper lobe, right lower lobe, aspiration pneumonia. Pulmonary congestion and edema. Brown atrophy of the heart and liver. Bilateral fibrous pleural adhesions. Status 10 years after appendectomy. Marked emaciation. Arteriosclerotic encephalopathy.

*Summary:* The patient presented the clinical picture of either anorexia nervosa or Simmonds' disease since the birth of her first and only child in 1908. About December 1935 the patient's symptoms changed definitely, chiefly in the appearance of severe transverse mid-chest pains which came on after eating. These pains disappeared temporarily, but returned in March 1936. The pain became so severe that she reduced even the small amount of food she ordinarily consumed. X-ray examination of the gastro-intestinal tract in June, 1936 showed only ptosis of the abdominal organs. She entered The Mount Sinai Hospital to be fed by duodenal catheter. During her stay she had severe paroxysms of coughing, and once or twice expectorated bloody sputum. At autopsy a carcinoma of the esophagus with perforation into the left main bronchus was found. No gross or microscopic lesion of the anterior lobe of the pituitary gland was found.

#### DISCUSSION

Simmonds in his original description of the disease in 1914 mentioned the amenorrhea, muscle weakness, dizziness, syncopal attacks, emaciation, rapid ageing, i.e., "senium precox", etc. The necropsy of this first case showed as the cause of death an almost total disappearance of the hypophysis, but the pancreas, thyroid gland, kidneys, adrenal and parathyroid glands showed no pathologic changes. The malady began after a puerperal sepsis and lasted eleven years. It seems to the author that it would be best to limit the term Simmonds' disease to this symptom-complex associated with significant pathologic change

in the hypophysis. The resemblance of the clinical picture of Simmonds' disease and of anorexia nervosa is sometimes striking, but is superficial; anorexia nervosa is now quite properly considered a psychosomatic disorder (10, 14). The few necropsies on anorexia nervosa that have been reported in the literature (11, 12, 13) do not reveal any significant changes, more especially none of the pituitary, to account for the symptoms. The two conditions, Simmonds' disease and anorexia nervosa, are in the opinion of the writer fundamentally different, in spite of the similarity of the clinical pictures which occasionally makes the differential diagnosis most difficult. One should always be critical in considering the possibility of merely functional endocrine disturbances without morphologic changes to explain syndromes, and one should be especially cautious in accepting the ingenious suggestion of Sheldon (15) that anorexia nervosa may be a functional Simmonds' disease—a pituitary "blackout", psychologic in origin. I agree at the present time entirely with the opinion expressed by Farquharson and Hyland (16) that the two syndromes may have a superficial similarity but are really essentially quite different. It is well, however, in the present state of our knowledge not to be too dogmatic. Even if anorexia nervosa is due primarily to some disorder of the subconscious mind that has destroyed the appetite, the consequent state of extreme undernutrition may be such that essential nutrient substances are not supplied to the body in adequate amounts for the elaboration of hormones. Which elements essential for the elaboration of such proteins may be lacking in states of extreme malnutrition are not known at present, but it is easy to theorize along such lines. The few published post-mortem findings in cases of anorexia nervosa which have come to autopsy do not describe secondary changes in the various ductless glands; that is they give no support for the belief in such a functional theory.

The differential diagnosis of Simmonds' disease and anorexia nervosa has been gone into thoroughly by competent observers (Richardson (17), Pardee (18), Farquharson and Hyland (16)) and will not be repeated here. On a statistical basis it is safer in the doubtful cases to diagnose anorexia nervosa rather than Simmonds' disease as the latter is much rarer than the former. In the case here-with presented the time and manner of onset, that is during the first puerperium in a woman of 33, the very low basal metabolic rates, the very low blood sugar level, the multiple attacks of syncope with injury, and the long duration of the anorexia in spite of some attempts at psychotherapy led or possibly misled several internists to the conclusion that the patient was suffering from Simmonds' disease rather than from anorexia nervosa. In view of the absence of any pathologic findings in the pituitary gland, one certainly should not call the condition Simmonds' disease; nor on the other hand, can one call the case one of anorexia nervosa unequivocally. As there is a whole group of such cases, perhaps fourteen in all, reported in the literature (9), I suggest the term pseudo-Simmonds' disease; this term is meant to include cases which had the typical clinical picture of Simmonds' disease, but in which the pituitaries were found to be normal. The term pseudo-Simmonds' disease would also include the possibility of a

functional Simmonds' disease without demonstrable morphologic abnormalities in the pituitary, should the future justify the acceptance of such a functional mechanism.

For the modern treatment of Simmonds' disease, particularly with testosterone the reader is referred to two recent papers on the subject (19, 20).

#### SUMMARY

A case is presented illustrating the superficial resemblance of the clinical picture of Simmonds' disease and anorexia nervosa, but the fundamental differences of the two disorders is insisted upon. At necropsy the adenohypophysis presented no abnormality, and for that reason the case should not be classified as an instance of Simmonds' disease. On the other hand, the case presented certain features and was so prolonged (28 years) that it could not be considered typical of the psycho-somatic disorder called anorexia nervosa. It is suggested for the present to designate all such doubtful cases as present the clinical picture of Simmonds' disease, but which at necropsy present no abnormalities in the pituitary gland, as pseudo-Simmonds' disease. There are about fourteen such cases already reported in the literature. If in the future there is evidence to justify the theory of a functional Simmonds' disease, the term pseudo-Simmonds' disease would also cover such cases.

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## THE COMMUNITY CARDIAC PROGRAM AND THE ROLE OF THE MODERN CARDIAC CLINIC\*

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During the past quarter-century, the diagnosis and treatment of heart diseases have undergone tremendous changes. It is a far cry from the days of the old medical dispensary where a "cardiac," anyone with a murmur or an irregular heart action, after a hasty, routine physical examination, was given his quota of tincture of digitalis, was told to go home, to stay home, and to "take it easy." As a result of group studies on the epidemiology, etiology, pathological anatomy and physiology of heart diseases, and as a result of an increased familiarity with modern implements of diagnosis, a new diagnostic and therapeutic approach has been evolved. In fact, the term diagnosis has given way to the more inclusive term appraisal, which implies an evaluation of the whole patient; and the term treatment to management, instituted and carried out according to a broad community plan. A cardiovascular disorder is now designated not by its leading symptom or physical sign but by a comprehensive clinical diagnostic pattern which embodies 1) the etiologic factor; 2) anatomic defect; 3) physiological aberration; 4) functional capacity; and includes 5) any related or unrelated accompanying disease or critical physiologic state.

Such diagnostic patterns have been in use for years and are now well-known. The following few are given as examples.

To indicate an acute recurrent episode in a rheumatic child whose heart already bears stigmata of previous attacks, the pattern may take the following form:

- (1) Rheumatic.
- (2) Mitral valvular deformity (M.I., M.S.)
- (3) Auriculo-ventricular heart block.
- (4) Moderate to marked circulatory insufficiency requiring complete bed rest.
- (5) Recurrent acute polyarthritis and carditis.

In an adult with chronic disabling rheumatic heart disease, the following diagnostic pattern may appear:

- (1) Rheumatic.
- (2) Mitral and aortic valvular defects (M.S., M.I., A.I.)
- (3) Auricular fibrillation.
- (4) Moderate to marked impairment of functional capacity, requiring partial bed rest.
- (5) Menopause syndrome.

Arteriosclerotic heart disease, depending upon the type and degree of cardiac involvement, may be expressed as follows:

- (1) General arteriosclerosis.
- (2) Coronary artery occlusion with healed infarction.

\* The subject matter relates to the evolution of a community program and clinic management for the care of indigent cardiac populations of large urban centers, taking New York City as an example.

- (3) Moderate functional limitation (angina pectoris when pace exceeds 2 min. per city block).
- (4) Irregular heart action—premature beats.
- (5) Diabetes Mellitus.

Obviously, there are many other patterns taking forms according to the several etiologic, anatomic and physiologic factors which enter into the clinical picture. They are intended to portray the cardiac problem in its broader aspects and to indicate avenues of therapeutic approach.

Preoccupation with patients in rounding out their respective diagnostic patterns soon leads one to a still broader outlook. Clearly, certain symptoms cannot be accounted for on the basis of the cardiac pattern alone. One is impelled, therefore, to appraise the patient in terms of his entire person and in the light of his complete environment. Such an appraisal discloses problems, which, for effective therapy, must be taken into account in the general plan of management. All problems, of course, cannot be solved but the physician who is aware of them is far more qualified to deal with the cardiac patient than the one who views him largely through the narrow chink of a stenosed valve or who interprets every one of his heartaches as an expression of coronary insufficiency.

A patient with heart disease is generally a disorganized person who carries a handicap under the constant fear of becoming uprooted. Management presupposes an understanding not only of the extent of his handicap but also of the nature of his other problems. This implies a therapeutic armamentarium with provisions for prophylaxis, health conservation and repeated physical, social, economic and emotional adjustments to enable him to carry on and thus afford him a meaningful life. He is not to be pampered, of course. The intention is to protect and guide the patient and to aid him to help himself. This, being the ideal, has not so far been fully attained. The aim, however, must be in this direction if the effort of those entrusted with the care of patients with heart diseases is to have any constructive meaning.

In order to avoid creating the impression that the care of patients with heart diseases is largely a matter of ameliorative therapy—to smooth their path to the grave, as it were—it is emphasized that their care embraces, in fact, a broad field of medical endeavor. Diseases that lead to cardiac affections are many and, not uncommonly, major diseases in themselves. Rheumatism, arteriosclerosis, syphilis and thyroid dyscrasias, are well-known examples. Heart involvement is an accompaniment or only a sequel which may be forestalled. Protection of the patient implies provisions to control the several etiologic agents whose repeated ravages are responsible for the cardiac injury and the progressive circulatory breakdown which may ensue. The cardiac damage, though generally important, is not always a primary concern. It may be minimal and clinically not at all apparent even in cases where a disease of known etiologic consequence has been in evidence for months or even years. Obviously then, the responsibility of anyone in charge of a large group of patients with heart diseases is not strictly confined to "cardiology." The responsibility has a broad medical basis with ramifications into the field of public health medicine.

By the same token, the term cardiologist is a misnomer. It implies a limitation in the function of a physician supervising patients with heart diseases whose interests and responsibilities extend, as a matter of fact, far beyond the immediate problems presented by cardiac defects. However, the term has been accepted and has apparently come to stay. For the purpose of this discussion, a cardiologist is primarily a clinician, an experienced internist or pediatrician who is familiar with the natural history of heart diseases and who, because of a special interest in the subject, has accepted the assignment of taking care of patients with cardiac problems. Such a clinician, by virtue of his interest, has presumably equipped himself with all necessary prerequisites for diagnosis and treatment in his chosen field and is proficient in cardiography, cardiovascular pathology and physiology and in the pharmacology of certain drugs employed in the treatment of patients with heart disease. He conducts research, not merely as a matter of intellectual curiosity, but with a conscious effort to solve problems which face him in dealing with his living patients.

Contact with patients and their manifold problems broadens his outlook and, aside from being a critical scientific inquirer, he soon becomes understanding, tolerant, mellow and human in his attitude toward the handicapped. He realizes that the etiology of diseases have multiple roots, some of which are traceable to environmental causes and that symptoms of patients with heart disease, therefore, are not always expressions of the cardiac defect. It is this realization that prompts him to reach out and attempt to elicit the aid of non-medical community agencies with a view to collaboration, to the end that the community may supplement his efforts. His aim is a broad community cardiac program with the hospital as the central unit, the cardiologist as coordinator, the public as collaborator and the patient as the principle concern.

This attitude already has brought about certain noteworthy results. The cardiac has gained in self-sufficiency and self-esteem. He is, in a measure, self-sustaining and less of a burden to himself, his family and to the community. His life has become more meaningful. At any rate, the cardiac child of today has been enabled to acquire an education; the adolescent and young adult is being prepared for a suitable vocation. Problems arising out of courtship, marriage, child-bearing and infant-rearing in the case of young adults are taken into account in the general plan of management. Adults of middle-age who have suffered an acute cardiac accident or those who have reached the stage of transient breakdown in circulatory efficiency are being adjusted by rehabilitation. Provisions have been made for the prolonged care of the subacutely ill, especially the rheumatic child. Custodial care is being instituted for the completely and permanently disabled adult. The profession has learned the important lesson that the care of a patient with heart disease is a continuous responsibility from the onset of his illness to the end of his day.

This implies a cardiac program of considerable magnitude requiring the joint resources and close collaboration of a variety of agencies. The collaboration is similar to that instituted for the tuberculous several decades ago, with the exception that the cardiac program, being an only recently explored field, is the more

immediate concern of the community. The care of the tuberculous has followed a well-established plan and the community program, as a result of effective public health measures and by virtue of the introduction of certain surgical treatments, has become a shrinking one. The care of the cardiac, on the other hand, is an expanding program with far-reaching possibilities. The efficiency of its service will depend upon the adequacy of organizational planning for effective collaboration among the constituent agencies of the community program. In part, it will depend also upon a proper allocation of responsibilities within the cardiac services of each individual, participating institution.

Participating medical agencies may be classed as the general hospital, hospitals for chronic diseases, sanatoria, convalescent homes and cardiac clinics. Collaborating community agencies are the public schools, vocational training centers, certain industrial establishments and voluntary associations organized to elicit public interest. These associations serve as bureaus of information and act as links in a chain of similar associations in other communities.\* By far, the most important medical agency is the general hospital with its wards, laboratories and particularly its cardiac clinics. Next in importance, would seem to be the hospital for chronic diseases, a second line of defense as it were, to take the load off the general hospital. Sanatoria meet the needs of a special group of rheumatic children during the protracted, smouldering phase of their illness. Convalescent homes are intended for the restoration of the cardiac patient to a degree of usefulness consistent with his handicap.

As indicated, these agencies have specific, singular functions unlike the general hospital where they are multiple and where, at times, they are less clearly defined. The actual contribution made by any one of them to the cardiac program as a whole will depend ultimately upon the size of the cardiac problem in the community and the provisions made, in facilities and personnel, to meet the responsibilities undertaken. Clearly, the roles of some agencies are more important than those of others no matter how efficient each may be in carrying out its own particular task.

The appraisal of the cardiac problem is beset with difficulties. In some sections of the country the problem seems negligible, while in others it is tremendous. For example, it has been found that presumably on account of certain geographic, climatic and social factors, the prevalence and clinical course of rheumatic heart disease differ widely. In Southern and Southwestern states the disease is mild and its course is often subclinical. Its prevalence is below one-half per cent the school population (1). In certain sections of the North, on the other hand, the disease is devastating in its effects. It produces extensive cardiac damage in more than four per cent of all children of public school age (2). In the states along the North Atlantic coast the prevalence rate is approximately the mean of these two extremes.

Taking heart disease as a whole, it has been estimated that in a city like New York, for instance, the adult population, young to middle-aged, is afflicted with

\* The New York Heart Association and the American Heart Association are examples, respectively, of such local and national associations.

heart disease to the extent of 20 per 1000 (3). This estimate, based on examinations of military service selectees, applicants for life insurance and industrial workers, presumably deals with employable adults in tolerably good health. Among adolescents and young adults as, for example, newsboys in New York (4), high school students in Philadelphia (5), and college students at Yale University (6), the prevalence has been estimated at 15 per 1000. Among public school children, according to the most conservative estimate, heart disease is present in approximately 7 per 1000 (7). Few attempts have been made to compute the entire cardiac population of large urban centers. In an inventory for New York City, about fifteen years ago, it was estimated that approximately 120,000 persons had heart disease (8).

All the foregoing estimates are probably understatements. They were computed on special, generally ambulant groups, such as school children and employable adults. They do not take into account the acutely ill at home or in hospitals, nor cardiacs, who, knowing that they were disabled, did not seek employment and, for one reason or another, did not attend public institutions. These estimates do not include the aged among whom heart disease is common but often concealed or just taken for granted as a part of the aging process. And, of course, there are no studies at all to indicate the prevalence of partially incapacitating coronary artery disease before the appearance of graphic stigmata, nor the prevalence of syphilitic aortic disease before anatomic changes become clinically discernible. There are no adequate data as to the incidence of hypertensive cardiovascular disease. In fact, there is no common agreement even as to what constitutes incipient arterial hypertension.

It would appear then, and mortality statistics tend to bear it out, that the prevalence of heart diseases in large cities along the North Atlantic coast, New York City being an example, is higher than any available estimates indicate. The actual prevalence is probably two or three times as high. There is a likelihood that some 300,000 persons in New York City require some measure of cardiac supervision and that two-thirds of these have to rely for most of their care on community service as implied by the cardiac program mentioned. The problem is obviously immense.

The machinery for the cardiac program has already been indicated. In order to appraise the relative roles of its component agencies, certain questions pose themselves with reference to their facilities and personnel. What provisions exist for the care of the chronically ill or the permanently disabled? What has been done for the rheumatic child whose vulnerability to the disease extends throughout the public school age and whose prospect for at least one major recurrence is approximately 65 per cent (9)? Is convalescent care, even in the ordinary sense, adequate for the purpose of rest and some measure of restoration of cardiacs who have weathered the storm? Is the general hospital equal to the task of meeting the needs of the acutely ill? How adequate is the clinic care of ambulatory cardiacs? Where and by whom are being determined the types of service a patient may require, from time to time, so as to meet his immediate needs and best insure the continuity of his supervision? What agency should be

regarded as the logical base of operation and coordination for services implicit in the cardiac program and what should be the standards of management of such an agency? Inadequate functioning on the part of any one of the several agencies would tend to impair the efficiency of the entire cardiac program, unless compensated by the acceptance of additional responsibilities by others. Actually, some agencies have not yet reached the stage of full maturity and their contributions have not been adequate. To compensate, other agencies have had to expand their functions.

Provisions for permanently incapacitated and aged cardiacs, for instance, have been meager. There are only a few institutions in the City of New York with accommodations for the "chronic and incurable cardiac." In such institutions, waiting lists are long and patients are often compelled to apply to crowded city hospitals never intended for this type of service. Since the Charters of these hospitals make it mandatory to accept "everybody," chronic cardiacs are accepted but promptly discharged at the first opportunity. Homes for the aged and infirm, where such patients might be cared for, are reluctant to accept them because they lack the facilities and the personnel to deal with the ever-impending emergency in cases of advanced heart disease.

Convalescent care is one of the great needs of cardiac patients. They may require it for the purpose of rest much the same as any average normal person, except that they are in need of it more frequently and for longer periods. They may require it when recovering from an episode of cardiac disability such as coronary thrombosis or congestive failure and when recovering from any other disease or from a surgical operation. Facilities for these services, especially for adult cardiacs, are limited. General convalescent homes are hesitant to accept patients with heart diseases because they are not prepared to deal with cardiac problems. They are justly afraid of cardiac emergencies and possible death which would disturb the equanimity of their organization. There is only one fairly large convalescent home in the vicinity of New York organized exclusively for adult cardiacs. However, this one, too, demands assurance that the applicant is "recovered," and that he can take care of himself. It is utterly inadequate to meet the needs of the very large group of indigent adult cardiacs in New York. Finally, there is the ever-present problem of placing racial and religious groups.

In the case of children, the situation is far more satisfactory. Their needs were recognized as early as 1920 when the first children's cardiac convalescent home was organized. Others soon followed. At present there are four convalescent homes in and about greater New York used exclusively for rheumatic children. Some of these have evolved into exemplary institutions not unlike sanatoria for the tuberculous. A better understanding of the clinical course of juvenile rheumatism has led to the realization that such patients require prolonged care. Some sanatoria now accommodate rheumatic children for periods from six months to two years (Table I).

This has been a great advance. However, the potentialities of these institutions have not as yet been adequately tapped. Being unattached, free-lance as

it were, sanatoria often choose their patients according to some particular study in which, for the time being, they seem interested and exclude others, who, in the judgment of qualified physicians, may be in need of prolonged institutional care. This, in a measure, has been unfortunate not only because it has interfered with the basic aim and smooth functioning of the cardiac program but also because it has led to frustrations on the part of some who, not realizing that sanitorial and convalescent care is only one of the endeavors of the cardiac program, had attached undue importance to their own function and, naturally, failed to live up to their own expectations. Some convalescent homes of the stature of sanatoria, after several years of existence have actually closed because, according to their own follow-up and statistics on the longevity of cardiac children under their care, they felt that they had made no effective contribution. Others have closed presumably because their funds had given out.

TABLE I

*Facilities for sanitorial and convalescent care of rheumatic children in New York City and vicinity\**

INSTITUTIONS	BED CAPACITY	PATIENTS AS OF JAN. 1, 1942	NEW ADMISSIONS	RE-ADMISSIONS	CENSUS FOR THE YEAR	DISCHARGES	PATIENTS AS OF DEC. 31, 1942	DURATION OF STAY (MONTHS)**			
								6 or less	6 to 12	12 to 24	24 or more
A	108	108	78	32	218	109	109	24	53	28	4
B	30	29	34	17	80	50	30	22	20	8	0
C	24	31	34	2	67	46	21	25	11	7	3
D	150	117	160	21	298	147	151	23	97	26	1
Total ....	312	285	306	72	663	352	311	94	181	69	8

\* Data obtained from the Annual Consolidated Statement of Cardiac Convalescent Homes, 1942. Compiled by the Committee on Convalescent Care of the New York Heart Association.

\*\* Out of 352 patients discharged during the year, 181, more than 50 per cent, were under medical supervision from 6 to 12 months and 69, approximately 20 per cent, from 12 to 24 months.

Obviously then, since several of the participating agencies have not as yet evolved into full-scale collaborators, the major task in carrying out a comprehensive cardiac program rests with the general hospital, its wards, laboratories, social service organization and its cardiac clinic. These divisions of the hospital have well-defined functions but their contributions are conditioned by their respective facilities and the nature of their assignments. As will be pointed out, the contribution of the general hospital to the cardiac program has been made largely through its cardiac clinic. This agency has been the very foundation of the cardiac program and has, since its inception, played a most significant role. The cardiac clinic has served as a base of operation and coordination of all major activities of the cardiac program.

This may seem strange to one not familiar with the management of a well-organized, modern cardiac clinic. There are still those whose view is tinged by

the dispensary odium, a hang-over as it were, and who, therefore, harbor the belief that the professional standing of the medical personnel and the diagnostic and therapeutic facilities of a "clinic" must, of necessity, be below the standards of the hospital ward. This view has been held, in part, because the more dramatic aspects of heart diseases, such as acute rheumatic carditis, coronary thrombosis and the more advanced forms of heart failure are encountered on the hospital wards. It has been held, in part also, because, up to recent years, the more spectacular implements of diagnosis such as the x-ray, electrocardiogram and facilities for functional tests, were available in hospital wards only. This outlook, though faulty, is understandable. The cardiac clinic of the past did not always possess the trained personnel nor the necessary equipment and often found it necessary to refer patients to the hospital ward for investigation and treatment. It is quite natural, therefore, that those not familiar with the personnel, facilities and equipment of the cardiac clinic of today should still look to the hospital ward as the most representative branch of the general hospital around which all activities concerning the care of cardiac patients should center.

Actually, what was true of the limitations of cardiac clinics in the past is not true today. It has not been true for years. Except for emergencies, requiring bed rest, minute observation and dramatic therapeutics, the modern cardiac clinic is equipped with all the necessary means for diagnosis and treatment. It has access to the same laboratory services as the hospital ward. The cardiac clinic, in fact, is the only agency in any general hospital where the more important, long-range problems of cardiac patients can be dealt with adequately. To fail to recognize this is to misdirect energy and hospital funds and to jeopardize the welfare of the patient. The systematic and continuous supervision of cardiac patients, a basic aim in the cardiac program, cannot be carried out unless the full potentialities of the cardiac clinic are recognized and effectively employed.

That the outlook which underrates the role of the cardiac clinic is fallacious is at once apparent if one realizes that in the lifetime of many cardiac patients, hospitalization is but an isolated incident and of comparatively short duration. It is the ambulant stage of heart disease which constitutes, by far, the longest period and it is during this stage that the cardiac clinic carries the greatest share of responsibility. It is not uncommon to find case histories, of rheumatic cardiacs, for instance, which date back twenty years or more, in the course of which hospital ward care did not exceed twenty days. Even cases of coronary thrombosis with myocardial infarction which are initially hospital problems, anywhere from four to six weeks, are successfully supervised, treated, guided and rehabilitated through the efforts of the cardiac clinic and are enabled to carry on for years.

More convincing in this direction is the function of the cardiac clinic in the care of the rheumatic cardiac child. It is common knowledge that in juvenile rheumatism, the disease often runs an insidious course without dramatic clinical manifestations. Even in the states along the North Atlantic coast, where the disease is regarded as virulent, the initial rheumatic episode is completely missed in approximately one-third of all rheumatic children and a cardiac valvular

defect is the first and only evidence of the disease (9). This is even more common, in fact, it is the rule, in Southern and Southwestern communities. Some children, having a tendency to a "smouldering" form of rheumatism, may go through life without a single major clinical episode but may develop, nevertheless, well-defined cardiac damage. They are seen but seldom, or not at all, on hospital wards until the age of adulthood, perhaps middle-age, some twenty or thirty years after the onset of their illness, when they first enter the stage of progressive heart failure. During all these years, however, if indigent, they do require the services of the cardiac clinic and the services of other agencies as determined by the cardiac clinic on the basis of certain medical, social or environmental indications. What is true in the case of the rheumatic child, is, in a measure, true of other groups. Any of them could be used to illustrate that problems in management during the ambulant stage of heart disease are manifold and that, in the long run, the responsibilities of the cardiac clinic outweigh, by far, the responsibilities of any other agency.

This is not to underrate the importance of the hospital ward. It is rather to define its role and to emphasize its limitations. In the care of patients with heart disease, the hospital ward has an important and highly specialized role. Indeed, its potentialities in meeting cardiac emergencies are unmatched by any other agency. This is its function preeminently and to this function, it is, in fact, strictly limited. It can serve in no other capacity. It certainly cannot assume the role of a coordinating agency in the cardiac program of the community. Its contact with the patient is all too brief. Even where the hospital ward has a "cardiac group" and an adequate social service organization to follow patients discharged from its service, in so doing, it is merely duplicating the work of the cardiac clinic and does it less efficiently. Such a cardiac group is essentially a study-group with a limited purpose. It can supervise only a limited number of patients and at intervals too long for proper observation. Because of this, it could not meet the needs of the community cardiac program.

At any rate, the medical staff of the hospital ward cannot be expected to deal with the broader problems of patients afflicted with such chronic and protracted diseases as the heart diseases. The hospital ward does not contact the majority of patients requiring care and when it does contact them, it is for too short a period and often too late for constructive management. As already pointed out, in matters concerning patients with heart diseases, the specific role of the hospital staff is to treat cardiac emergencies. This is the recognized domain of any experienced internist. Under the supervision of the attending staff, responsible medical residents can treat and, in fact, usually do treat, in every well-governed hospital, all acute diseases including diseases of the heart. This does not mitigate against the role of the specialist or the value of his collaboration with the medical staff. A specialist in heart diseases has a well defined role. He is in charge of a cardiac clinic primarily and is therefore in active charge of the patient before and immediately after the hospital ward had performed its specific task and had released him. He should, of course, follow the progress of his patient on the hospital ward and collaborate whenever called upon to do so.

The patient, however, remains under the jurisdiction of the attending medical staff.

For the purpose of better organization of the cardiac service of any general hospital, then, the function of each constituent division should be clearly defined. Responsibilities should be assigned in the light of such well defined functions and support given in proportion to responsibilities assigned. In this way, the general hospital, the logical center of activities of the community cardiac program, will have firmly established its own machinery for effective participation. Proper allocation of responsibilities leads to an economy of effort and affords more adequate service to the patient.

There is another, perhaps a better and more practical reason why the general hospital should confine its function to emergencies and look to its cardiac clinic as a major division to carry its cardiac program and to represent it on the com-

TABLE II  
*Hospitals in New York City with medical and pediatric beds assigned, 1934\**

BOROUGH	NUM- BER OF HOSPI- TALS	VOLUN- TARY	MUNICI- PAL	FED- ERAL	TOTAL BED CAPACITY	MEDICAL BEDS		PEDIATRIC BEDS	
						Number	Per cent	Number	Per cent
Manhattan.....	29	23	5	1	13,304	2,424	18.2	892	7.4
Bronx.....	6	2	3	1	2,521	872	34.5	110	4.4
Brooklyn.....	21	17	4	0	7,479	1,325	17.7	451	6.0
Queens**.....	4	4	0	0	625	107	17.1	21	3.5
Richmond.....	4	3	0	1	952	216	22.7	141	14.8
Totals.....	64	49	12	3	24,881	4,944	19.9	1,615	6.5

\* From, *Facilities in New York City for the Care of Patients with Heart Diseases*, Prepared for the Hospital Survey by the New York Heart Association, 1936.

"... only the hospitals listed by the office of the Hospital Survey as having beds definitely assigned to the children's medical service and the adult medical service, are counted on this table."

\*\* Since this survey was made the borough of Queens acquired a large municipal hospital.

munity cardiac project. Investigations have revealed that, on the whole, ward facilities for cardiac patients are so limited that other services must be provided to compensate for this inadequacy. In a recent study of existing hospital facilities in the City of New York for patients whose primary or only disability is heart disease (10), it was estimated that out of a total of 92 hospitals where patients with heart diseases were admitted, only 64 had beds assigned to medical or pediatric use and that only about 25 per cent of the total bed capacity of these 64 general hospitals was assigned to such use.

Table II shows the distribution of these hospitals in greater New York and their respective medical and pediatric bed capacities (medical 4,944; pediatric 1,615; total 6,559). Furthermore, if all 92 hospitals surveyed were to assign 25 per cent of their total bed capacity to medical and pediatric use, approximately 7,200 beds would be available at best. It should be noted that these beds are

only assigned, and this only by a portion of the hospitals so that it is not possible from these figures to be certain as to what number of beds are actually available to general medical services. As to beds available for cardiac patients there is no index at all. Relying upon one's own experience, however, and remembering the reluctance with which the general hospital admits the "incurable" cardiac and how often admission is refused, one cannot escape the impression that hospital care for patients with heart diseases, even the most hospital-worthy, is not readily available.

It is unfortunate, in a measure, that hospitals have never prepared to meet the requirements of this important group of seriously ill patients. It is common knowledge that patients with heart diseases when requiring hospital care are in urgent need of it and their recovery is often a matter of several weeks to several months. A patient with acute rheumatic carditis, coronary thrombosis or heart failure from any cause cannot be restored even to a reasonable degree of health and comfort as quickly as those with other medical diseases. If the hospital

TABLE III

*Duration of hospital stay of patients designated as cardiac on their discharge from voluntary and municipal hospitals in New York, 1933\**

AGE GROUP	DIS- CHARGED	NUMBER OF DAYS IN HOSPITAL				
		1-7	8-14	15-30	31-60	Over 60
Under 14 yrs.....	2,181	504	396	541	414	326
Over 15 yrs.....	27,367	8,075	6,356	7,093	3,569	2,274
Not reported.....	104	42	18	21	13	10
Total.....	29,652	8,621	6,770	7,655	3,996	2,610

\* Data obtained from, Facilities in New York City for the Care of Patients with Heart Diseases, Prepared for the Hospital Survey by the New York Heart Association, 1936.

stay is too short, recovery may be incomplete, and unless supplemented by additional care on the part of another competent agency, repeated hospitalization may become necessary for the same single illness. Actually, the duration of hospital stay for cardiac patients is too short.

A study of hospital discharges in voluntary and municipal hospitals of the five boroughs of New York City for 1933 disclosed that in the case of approximately 30,000 patients designated as cardiacs, the average hospital stay was 21 days and that 50 per cent had been hospitalized for only two weeks or less (11). It is especially noteworthy that figures regarding the duration of hospital stay are substantially the same for children under fourteen years of age as for older age groups (Table III). Assuming that patients discharged with the diagnosis of heart disease were admitted because of the need of some treatment—and one can hardly question this assumption in the case of children under fourteen years of age who fared no better than the adults—their discharges on an average of 21 days and in 50 per cent of cases in 14 days or less, is a striking illustration that the general hospital ward is not equipped to meet the needs even of the acutely

ill cardiac. Clearly then, the hospital ward has its own dilemma in meeting its specific obligation to provide for cardiac emergencies and is not in a position to assume jurisdiction over the care of the cardiac population.

In order to make an effective contribution to the community cardiac program, the general hospital must reorient its cardiac service so as to fit it into the broader scheme of the community project. To collaborate effectively, it must create the machinery for collaboration. To this end it can develop an appropriate division of its cardiac service to deal with its own cardiac problem and to represent it on the community program. It should be emphasized that collaboration on the part of the hospital with a community program is not a unilateral gratuity. In helping to build a strong community cardiac program, the hospital will be amply compensated. The community program, having as its basic aim, the uninterrupted supervision of patients with heart diseases, will eventually develop agencies that will supplement the general hospital by continuing the care of the cardiac patient. Continued care by qualified agencies outside the hospital ward must, of necessity, reduce hospitalization. This, in a measure, has been already accomplished.

Since the general hospital is a beneficiary of such a program, the need for its collaboration is self-evident. What, then, should be its machinery for adequate collaboration? The hospital ward service obviously cannot take on the task. As pointed out, its contact with patients in terms of time is inadequate. It need hardly be stressed that the so-called cardiographic laboratory is a service-station to hospital wards and cardiac clinics and, as such, has no part in the treatment of patients. Clearly then, the cardiac clinic would appear to be the only agency within the hospital organization to take active charge. The cardiac clinic can serve as a base of operation and coordination for the cardiac program within the hospital and by virtue of its close contact with other components of the cardiac program, it is the logical agency through which the general hospital can effectively collaborate with any broad community cardiac project. As such, the cardiac clinic should be developed and supported as a major division of the hospital organization. For, upon its proper management and adequate functioning will depend the efficiency of the cardiac service within the hospital and the successful evolution of a comprehensive community program for the care of patients with heart diseases.

The modern cardiac clinic is an outgrowth of more than thirty years of serious effort on the part of physicians, social service agencies and voluntary groups in behalf of the ambulant cardiac patient. According to available records (12), the first clinic was organized in 1911 as "The Bellevue Hospital Social Service Cardiac Clinic for Working Adults," by Dr. Hubert V. Guile at the suggestion of Miss Mary E. Wadley, the head of the social service department. It was she who recognized that scores of cardiacs discharged from the hospital required assistance in convalescent care and occupational rehabilitation. She insisted, however, that for effective assistance, continuous medical oversight was imperative. In 1919 the clinic was taken over by Dr. John Wyckoff, who perhaps more than anyone else, pointed out the utility and advantages of cardiac clinics. The

clinic was organized in the belief that the number of returns of cardiac patients to the wards could be appreciably diminished if, on discharge from the hospital, they could be cared for in a special clinic manned by physicians who were interested and who were qualified to deal with their problems (13).

These pioneers, whose insight and interest led to the establishment of the first cardiac clinic served, in fact, to institute a new era. They shed new light on the basic need of patients with heart diseases, namely, their need for continuous care and introduced a type of management to meet this requirement. They set in motion latent energies on the part of the medical profession and the public, which, in the course of subsequent years was to culminate in a broad community cardiac program. Within a span of five years, more than twenty cardiac clinics were established in New York City alone. The majority of these clinics soon realized the need for mutual aid and, as early as 1917, formed an Association of Cardiac Clinics the purpose of which was to exchange information, formulate diagnostic criteria, improve clinic facilities and establish standards of clinic management. By this time, another organization under the pretentious name of Association for the Prevention and Relief of Heart Diseases was in existence about two years. Although its functions were not clearly defined, it served a useful purpose in public relations. Its development was interrupted by the first World War. When reorganized in 1919, however, it undertook an ambitious program, absorbed the Association of Cardiac Clinics, extended its interests to convalescent care and vocational guidance and instituted studies on the needs of the cardiac child at school.

The merger of these two organizations laid the foundation of the present New York Heart Association,\* a voluntary organization the basic aim of which has been to bring together in cooperative effort, physicians, social service agencies and public spirited lay-groups with a view to affording patients with heart diseases the best possible care which the accumulated experience of the medical profession and sound public health organizations have to offer. Since its inception, the New York Heart Association has been a moving spirit in developing a community cardiac project. It has been promoting a broad educational program for physicians as well as the public and, through a voluntary affiliation with a majority of general hospitals and allied institutions in greater New York, has been instrumental in exerting a guiding influence on the organization and management of their cardiac services. It has served, throughout the years, as a clearing house of information on all matters pertaining to the care of patients with heart diseases.

The Association is governed by a Council of physicians of recognized standing in the special field of cardiovascular diseases. It functions through a group of Executive Committees, whose activities are concerned, respectively, with research, cardiac clinic management, sanitorial and convalescent care, criteria and nomenclature, cardiac children at school, cardiacs in industry, scientific programs, community planning and public education. Several of these committees

\* For several years, the New York Heart Association has been designated as the Heart Committee of the New York Tuberculosis and Health Association.

have made noteworthy contributions. The Committee on Research has completed a fifteen year study on the natural history of rheumatic heart diseases (14). The Committee on Criteria and Nomenclature has published the fourth edition of a monograph on diagnostic criteria in cardiovascular diseases (15). The Committee on Cardiac Clinics has formulated standard requirement for cardiac clinic management (16). These standards have been in use as the accepted guide in 63 affiliated clinics\* in New York City alone by 1941 (Table IV). They have been adopted in recent years also as a pattern for clinic standards in other fields of medical endeavor.

A cardiac clinic, then, managed in accordance with standards evolved in the course of approximately thirty years of cumulative experience and operating in close collaboration with all other agencies concerned with the care of patients with heart diseases, would seem qualified to play a major role in the cardiac service of a general hospital and to represent it on the community cardiac program. Mem-

TABLE IV  
*Composition of case load and clinic personnel of 63 cardiac clinics affiliated with the New York Heart Association, 1941\**

CASE LOAD	ADULTS	CHILDREN	TOTAL	CLINIC PERSONNEL	
Beginning of Year.....	12,248	6,656	18,904	Physicians.....	482
New Admissions.....	2,799	1,095	3,894	Nurses.....	101
Readmissions.....	199	108	307	Social Workers.....	61
Census for the Year.....	15,246	7,859	23,105	Clerks.....	44
Discharged, Transferred, Lapsed.....			5,710	Volunteers.....	66
End of Year.....			17,395	Total.....	754

\* Figures obtained from the Summary of Clinic Reports, Committee on Cardiac Clinics of the New York Heart Association, 1941.

bers of the medical profession, particularly those in charge of medical and pediatric divisions of hospitals, might avail themselves of the potentialities of this agency and utilize its service more fully, in the care of the cardiac population in their respective communities. It is on this assumption that the organization, personnel, facilities and operation of the modern cardiac clinic will be described in some detail.

A modern cardiac clinic, in conformity with standard requirements, is an integral part of the general hospital and operates as a special section of its medical or pediatric division. It serves to continue the care of patients discharged from hospital wards and to supervise the management of other ambulant patients with cardiovascular diseases who may apply and who, according to the policy of the hospital in question, are eligible for admission. Such a clinic has ward service

\* These clinics are affiliated, on a voluntary basis, with the Committee on Cardiac Clinics of the New York Heart Association under conditions set forth in its Standard Requirements.

available for the study and treatment of its patients whenever they require hospitalization.

The medical staff of the clinic consists, in the main, of physicians who have been trained for their task and who are familiar with the cardiac problem. Exceptions, in this respect, are physicians referred from other departments of the hospital for short periods, three to six months, as a part of the general medical training. The clinic does not permit itself to be used as an anchor of attachment to the hospital, by any physician.

The Physician-in-Charge of the cardiac clinic, or Chief of Clinic, is generally an internist or pediatrician who, by virtue of length of service and recognized ability, has merited the rank of associate, or at least that of assistant physician, and who has had two years or more of special training in clinic management in an approved cardiac clinic.\*

The Chief of Clinic is in complete charge and is fully responsible for the management of his clinic. His responsibilities entail all matters relating to admission of patients, initial diagnosis and treatment, subsequent changes in diagnosis or treatment, interdepartmental consultations, hospitalization, problems pertaining to school and vocational adjustment, transferring patients to or receiving patients from collaborating agencies and the disposition or final closing of all records. Less specified but equally important are his duties in arranging timely conferences with social service, clinic conferences with his medical staff, supervising clinic and laboratory procedures and training of assistants. These responsibilities require his presence on all clinic-days and during the major part of all clinic-sessions. He may assign some of his manifold duties to qualified senior assistants for whose decisions, however, he is always responsible.

For the proper functioning of an organization so complex as a cardiac clinic an adequate staff is essential and regular and prompt attendance is imperative. Aside from unforeseen problems which commonly arise in the course of a clinic session, the routine care of patients is, in itself, time-consuming. Experience has taught that the interval history and examination of a return patient, requires, on the average about twenty minutes and the examination of a new patient, a half-hour or more. This means that a member of the cardiac clinic staff cannot conveniently examine more than six patients in the course of a two-hour session. Since the Chief of Clinic, who is ultimately responsible, must always be appraised of all new diagnostic and therapeutic problems, the procedure may become even more time-consuming. With a case load of fifty patients per session, then, a cardiac clinic requires a staff of not less than ten physicians for routine examinations alone.

However, a well governed cardiac clinic does not confine its function to routine work alone. The Chief of Clinic and some of his senior assistants are often preoccupied with patients referred in consultation. Others are assigned to fluoroscopy, electrocardiography, functional tests or some special therapy. Still others devote part of their time to studies on problems of special interest.

\* An approved cardiac clinic is one that operates in conformity with the Standard Requirements. It is generally an affiliated clinic.

As has been intimated, certain clinic sessions are apt to present unusual medical and social problems. A patient emerging from an acute episode of illness may require further institutional supervision; another may have become acutely ill and in need of hospital care. A cardiac with a guarded prognosis may have been advised surgery or a cardiac mother who has become gravid, a therapeutic intervention. Some of these are weighty problems and every decision entails responsibilities. When a decision has finally been made, there is still the question of placement. Assuming that the patient is "suitable," for ward service, are beds available in the parent hospital? If not, to whom should the task in question be entrusted? What is the risk in disposing of the patient into quarters unknown? Is there any risk in waiting? Should domiciliary care be provided and how? Are the services of a district physician or a district nurse available? If not, is there any prospect that some member of the clinic staff may volunteer his services? These are problems of great moment, demanding prompt solution.

Then there are the problems of lesser urgency arising from environmental factors, the home, the school and the workshop. Patient A cannot accept the way of life of his growing children and meets their challenge by increasing symptoms of dyspnea and precordial pain. Patient B, a rheumatic child, has not been at school an entire semester because he cannot conveniently climb four flights of stairs several times a day. Patient C who has recently recovered from a cardiac injury cannot return to his former occupation and requires vocational retraining. Such environmental problems are the concern of the medical staff of a cardiac clinic because they may confuse diagnosis, vitiate therapy and influence prognosis.

The clinic staff, too, has its own problems. Cardiology is a dynamic specialty. Aside from experiences gained through years of diligence in attending patients, staff members, in order to keep abreast with advances in their chosen field, must be in touch with all current developments in clinical and technical procedures pertaining to diseases of the heart. To this end, the clinic chief assigns them successively to follow cases admitted to the wards and to present reports on their progress to the clinic staff at stated conferences. Journal club meetings are arranged for a critical review of current literature.

In addition to an adequate medical staff, a cardiac clinic must have access to other services. Consultations must be available in all specialties, particularly in dentistry, rhinology, otology, metabolism and nutrition and ready access must be had to laboratories and a pharmacy. During clinic sessions, the services of a graduate nurse or a qualified student nurse are required to help the medical staff. The nurse is in charge of supplies, keeps examining rooms in order, drapes female patients, prepares hypodermic medications and assists in procedures such as venipuncture and thoracic or abdominal paracentesis.

A well-trained social worker is indispensable to the operation of a cardiac clinic. Her responsibilities are next only to those of the Chief of Clinic. Since cardiac clinic sessions are conducted at stated intervals, two or three times a week at best, and, since it is axiomatic with the cardiac program that the care of patients with heart disease be continuous, the cardiac social worker is actually in

charge of the patient during the absence of the clinic staff. She is always on call. The major objectives recognized so far as appropriate to hospital social service have been defined and are well known (17). These objectives are, however, general and do not quite define the role of the cardiac social worker. With the exception, perhaps, of a clinic for the tuberculous, no agency deals with patients so much in need of uninterrupted care as the cardiac clinic. There is not a single factor in the life of a cardiac which may not be pertinent in the appraisal of his symptoms. Interval histories do not always reveal these factors. It is the cardiac social worker, providing she has successfully cultivated the role of a confidant and has become familiar with the environment, who alone can bring them to the attention of the examining physician. It is a part of clinic management that the social worker visit the home of every new patient, complete a social history-form and attach it to the medical records. She is to revisit as often as she may deem it necessary or whenever the Chief of Clinic may require additional information.

Because of her intimate familiarity with patients and their environment, the social worker is the first to be aware of their maladjustments, be they medical or any other. She is most qualified to assign patients to the several divisions of the clinic where their problems are most likely to be met. She is the logical supervisor of the cardiac clinic, yielding to the nurse-in-charge, if one be present, only in the supervision of facilities. She is present at every clinic session and during the entire session, participating in all deliberations concerning the management of patients. The social worker interviews all new patients on their initial visits and all return patients as necessity demands. She keeps records of clinic visits and return appointments so that she may determine the cause of any lapse in attendance. She assists the medical staff in arranging for hospitalization, convalescent care, opportunity school classes and vocational rehabilitation.

It is through the social worker that the cardiac clinic maintains contact with all other agencies. She is responsible for sending of reports, transcripts of records and for all correspondences in dealing with collaborating institutions. The cardiac social worker keeps records of active and inactive patients, admissions, attendance, transfers, discharges and social service visits. These are recorded on schedules devised by the Committee on Cardiac Clinics of the New York Heart Association and a copy is submitted monthly to its Executive Secretary, to serve, in conjunction with records submitted by other clinics, as material for study and information in the community cardiac program.

Although it is understood that the cardiac social worker is responsible primarily to the Director of Social Service of the hospital, in matters relating to the patient's health, she can serve best by dealing directly with the Chief of Clinic. The recent trend to regard Social Service as a special department which is to serve clinics in consultation only, is objectionable from the point of view of cardiac clinic management. Social service is an integral part of cardiac clinic organization and its worker is an indispensable member of the clinic personnel. Proper integration of her functions with those of the medical staff is essential to the successful operation of a cardiac clinic.

In order that a cardiac clinic with its complex organization, consisting of medical, nursing and social service staffs, statistical clerks and research groups, may function adequately, certain basic facilities and equipment are necessary. A spacious, well-ventilated waiting room, separate examining rooms for male and female patients, office space for the social worker to afford privacy in interviews and a suitable conference room for the medical staff are basic facilities. Major equipment includes an electrocardiograph, fluoroscopic unit, basal metabolism apparatus, spirometer, scales and measuring rod and implements for a variety of functional tests. It is essential that a clinical laboratory and a pharmacy be within easy reach and that an emergency tray be on the premises. Each examining room is an individual unit, furnished with a large examining table, desk and accessories, flashlight, otoscope, ophthalmoscope, tongue depressors, thermometer and sphygmomanometer. Spacious quarters with office spaces for interviews and conferences and individual examining rooms separated from the waiting room are intended to afford an atmosphere of quiet, so necessary in a clinic where auscultation is an important part of physical examinations. The equipment enumerated is essential to clinic self-sufficiency and economy of effort.

In the realization that a cardiac clinic has a highly specialized function, its medical staff attempts to limit the enrollment of patients to such numbers as can be given adequate care. Patients are admitted only when referred by reliable agencies and when there is reasonable assurance that a cardiac problem exists. General medical or pediatric clinics, hospital ward services, admitting physicians, private physicians and cardiac clinics of other hospitals are acceptable sources of reference. The Chief of Clinic or a senior assistant designated by him determines eligibility for admission.

Three categories of patients comprise the case load of a cardiac clinic as follows: Patients with, 1) well-defined organic heart disease; 2) "potential heart disease" and 3) "possible heart disease." The term "potential" refers to patients who have no discernible cardiac defect, but who, having suffered an attack of a disease such as rheumatism, may, by virtue of the recurrent nature of the disease, develop heart involvement in the near future. The problem in this group is essentially that of prophylaxis. The term "possible" refers to patients who present abnormal but inconclusive physical signs. These are observed for further evidences which might confirm or rule out heart disease. A patient may at times be designated as both a "potential" and a "positive" cardiac. A child with a clear-cut rheumatic history but inconclusive physical signs is an example.

Another class of patients seen at the cardiac clinic are those referred for "opinion only." Such patients, referred in consultation by other departments are not enrolled unless conclusive evidences of heart disease are discovered and then only if the referring clinic agrees to a "request for transfer." Enrollment of children is governed by the pediatric age limit determined for the hospital wards. Once admitted, however, the children's cardiac clinic may carry them beyond the specified pediatric age, perhaps through the high school age, for the purpose of observation and study. In cases of adults who have been enrolled in a cardiac clinic but whose attendance at another clinic is equally important, responsibility

is shared jointly by both clinics. A syphilitic with aortitis or a diabetic with coronary artery disease are examples.

The procedure on admission to the cardiac clinic is much the same as that of any other well established diagnostic clinic. The patient's history is taken and a complete physical examination is made. Initial laboratory studies include urine, blood, fluoroscopic or x-ray and electrocardiographic examinations. In the final appraisal of the patient, which usually requires three successive clinic visits, social service records, and hospital charts, if any, are taken into account. Return visits to the clinic are arranged by appointment, anywhere from three days to three months, depending upon the urgency of the patient's complaints. However, when symptoms warrant, a patient may visit the clinic at any regular session. Every return visit entails a careful interval history, a complete physical examination and such laboratory studies as may be indicated. If the patient's disease-pattern belongs to a category for which a special study or treatment group exists, he is assigned to that group.

Patients who are acutely ill or who present problems not quite within the realm of clinic routine, are brought to the attention of the Chief of Clinic. If there is disagreement in diagnosis or treatment or if new findings warrant a change in the diagnostic pattern, the procedure is similar. In cases where the clinical picture is too complex for immediate decision or in cases of unusual interest, a conference is held for the purpose of critical discussions and the instruction of less informed members of the staff.

The records of a cardiac clinic conform to the standard charts provided by the New York Heart Association. These are essentially fact-finding charts in which all significant points in the initial history, physical examination, social history, return visits and laboratory reports are recorded in appropriate columns which lend themselves to rapid review or tabulation. In such records, because of an orderly arrangement of data, the frequency of any significant complaint, physical sign or laboratory finding, even in the course of several years, may be traced readily within a few minutes. The reverse of each chart-form is blank and is used for notations or periodic summaries of the patient's case record. The narrative form of charts employed in general clinics are of little use in a cardiac clinic. They are too fragmentary, often illegible and do not reveal the true, long-range clinical picture of heart diseases.

The terminology employed in recording data on clinic charts as well as the criteria used in formulating diagnostic patterns conform, in every well-governed cardiac clinic, to the nomenclature and criteria provided by the New York Heart Association in its well-known monograph on the "Criteria for the Classification and Diagnosis of Heart Diseases."

Such is the plan of organization, management facilities and procedure in a modern cardiac clinic. The standards by which it is guided are the result of years of conscious effort to promote efficiency in keeping with increasing responsibilities. The importance of its service to patients lies not only in the fact that it provides intimate contact over long periods and thereby renders timely aid but also in the fact that, when functioning adequately it can influence the course of

heart diseases and can, in a measure, reduce the need for the services of other institutions. As has been pointed out, in the present state of development of the community cardiac program, the facilities of hospital wards, sanatoria and convalescent homes are often inadequate even for their comparatively limited assignments. To enable them to function with some semblance of efficiency, while striving to develop into full-scale collaborators, the need for their services must be curtailed and kept within the range of their existing capacities. In this direction, the cardiac clinic can serve most effectively.

Actually, the cardiac clinic has already taken over some of their functions. Some clinics have organized domiciliary care for rheumatic children during the subacute or smoldering phase of their illness, thereby sharing in the task of sanatoria. In many cases, the treatment of adults with chronic heart failure, who rightfully belong to hospitals for chronic diseases, has been taken over by the clinic. Finally, it is the accepted role of the cardiac clinic to determine the type of accessory service required by the patient and to place him under the temporary care of an appropriate collaborating agency, if and when such service is available. The cardiac clinic functions as the hub around which revolve most of the activities of the community cardiac program.

Aside from its accepted role as the agency in charge of ambulatory cardiac patient and its less defined but equally important function as the base of operation in the cardiac program, the cardiac clinic has evolved an ideal set-up for teaching and research. Its organization, facilities and its records, particularly those containing data over the years, lend themselves admirably for large-scale group studies. The hospital ward, the sanatorium and convalescent home deal with the exceptional aspects of heart diseases. These are incorporated in the records of the cardiac clinic as incidents in a long chain of events which, in the aggregate, constitute the disease patterns. The cardiac clinic is the only agency where the whole clinical picture of the cardiac patient is unfolded and the natural history of the several heart diseases fully revealed.

Although the community cardiac program is similar to the community plan for the tuberculous, its motivation was different. In the case of the program for the tuberculous, the community attitude was, in a large measure, defensive. Dealing with a communicable disease, the community, as a matter of self-protection, made provisions for its control. In the case of heart diseases, rheumatic heart disease in particular, the community attitude was essentially a challenge against a scourge whose ravages took a heavy toll of children during their formative period and of adults during their most productive years. It was an aggressive attitude with a strong emotional component, clamoring for prevention and relief. The participation of the medical profession and its critical appraisal of the several aspects of the cardiac problem, from time to time, has led to a planned program for the care of the cardiac population.

The community cardiac program, is, of course, still in the process of evolution. However, its basic aim has been clearly defined, and has, in a large measure been realized. Its aim has been to provide and adequately develop a group of agencies for the purpose of prevention, health conservation, adaptation and relief with a

view to affording patients with heart diseases a continuous supervision. The cooperative effort stimulated by this community cardiac program has resulted in a better understanding of the natural history of heart diseases on the part of the medical profession and a systematic and more adequate care of patients with heart diseases.

#### SUMMARY

As a result of the evolution of a broad community cardiac program during the past twenty-five years, the management of patients with heart diseases has changed radically. Diagnosis is now expressed in terms of comprehensive patterns which identify the patient with well-defined clinical categories and treatment is conducted by a group of collaborating agencies.

The community endeavor has been to provide for patients with heart diseases the best possible care which the accumulated experiences of the medical profession and the joint efforts of a group of sound public health organizations have had to offer. In this direction, continuous supervision has been a basic aim of the cardiac program.

Participating medical agencies are the general hospital, hospitals for chronic diseases, cardiac clinics, sanatoria and convalescent homes. Collaborating non-medical agencies are public schools, vocational training centers, certain industrial establishments and voluntary associations consisting of professional and non-professional groups interested in the cardiac problem.

By virtue of responsibilities which extend over the ambulant stage, the longest period in the life of the cardiac patient, the general hospital, through its cardiac clinic, has been serving as the base of operation and coordination of all activities concerning the medical care of patients.

Voluntary groups, such as local and national heart associations, have been instrumental in formulating plans for collaboration among the component agencies of the community cardiac program and have developed criteria and standards of management for the several participating institutions. The medical membership of these associations consists of physicians who have had years of contact with the cardiac problem. The majority of them are chiefs of cardiac clinics.

The modern cardiac clinic is an outgrowth of approximately thirty years of cumulative experience and operates in accordance with accepted standards of management. By virtue of its control over the patient from the onset of his illness to the end of his day, its responsibilities outweigh, by far, those of any other agency. Its organization, personnel, facilities and plan of operation have been adequate to meet most problems facing patients with heart diseases.

The services of hospital wards, sanatoria and convalescent homes, though important and at times indispensable, are of comparatively short duration, and are, therefore, strictly speaking complimentary services in the long-range plan of community care of cardiac patients. These agencies deal with the exceptional aspects of heart diseases which may or not appear during the lifetime of the patient. It is the cardiac clinic where the whole clinical picture of the cardiac patient is unfolded and the natural history of the several forms of heart diseases fully revealed.

Active support of the community cardiac program and a more complete utilization of the potentialities of the modern cardiac clinic will lead to a better understanding of the cardiac problem by the medical profession and will afford a more adequate supervision of the large indigent cardiac population entrusted to its care.

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# HEMORRHAGIC OVARIAN CYSTS AND MENOMETRORRHAGIA ACCOMPANYING THROMBOCYTOPENIC PURPURA HEMOR- RHAGICA AND NECESSITATING HYSTERECTOMY IN A YOUNG WOMAN

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Uterine bleeding may occur in the course of a chronic cytothrombopenic purpura hemorrhagica by the same pathologic process as bleeding from the mucosa of any other organ or body cavity. In the past four years I have encountered two such cases in which menorrhagia developed some time after the diagnosis was established and the disease assumed chronic status. The pelvic findings were negative and no gynecological operation was found to be necessary.

However, another case was encountered more recently in which gross pelvic lesions were present that could by themselves account for the menometrorrhagia. Major surgery was resorted to in this case before the true nature of the hemorrhagic diathesis was determined. This third case is the basis of the present report.

## CASE REPORT

*History:* The patient, a young woman of 25 years, married 5 years, has one child 3 years of age, had no other pregnancies. Since the age of 10 years she noticed petechiae on the least trauma and intermittent nose bleeds including one attack during her only pregnancy. This tendency had stopped for 2 years following nasal cauterization. She had no serious illnesses. Her menses began at 12½ years of age, were regular of seven days duration with the tendency to be profuse the first two days and accompanied by the passage of clots. When she was deflorated she bled for a month continuously; the hymen had to be cauterized to stop the bleeding. She passed through an apparently normal parturition and puerperium.

For three years before the birth of her baby she was subject to recurrent attacks of pain in the right lower quadrant, accompanied by nausea and vomiting. The attacks recurred on two occasions, four and two weeks prior to examination. They then became more frequent and were followed by dizziness and weakness but no syncope.

*Examination* (October 23, 1941). The patient was pale, but well nourished with negative general physical findings. Gynecologic investigation disclosed the following: The introitus was somewhat tight, the uterus was well forward; the right pelvis was occupied by a cystic tender moderately movable mass which was elongated. A routine blood examination revealed a severe anemia. The history had not suggested any connection between the pelvic lesion and an abnormal blood condition except that the anemia was thought to be due to the uterine blood loss. Further routine blood studies were carried out as shown in Table I.

*Operation:* On November 4, 1941, a right salpingo-oophorectomy and appendectomy was done through a median hypogastric incision. The bloodless appearance of the abdominal wound was particularly noteworthy. The right ovary was found to be converted into multilocular cysts altogether enlarging it to the size of a large pear. It was slightly bluish in color. There was some blood-stained fluid in the pelvis. The tumor was adherent to the broad ligament and the right uterine wall. It was liberated and removed. The appendix was also removed. A number of approximating sutures were required to control oozing from the broad ligament surface, and a Penrose tube drain inserted down to its depth, followed by a typical abdominal wound closure.

The surgical specimen consisted of a Fallopian tube which measured 6 cm. in length and showed no gross abnormalities. The ovary was enlarged and converted into an irregular cyst, which was ovoid in shape, measured 9 cm. in long diameter, 6 cm. in transverse diameter; the outer pole was purplish in color. The entire cyst was smooth. On section the inner aspect of the mass was made up of two separate cysts. The inner lining of the cyst was smooth but covered by brownish chocolate-colored adherent material. There were no excrescences. The smaller cyst appeared to be a hemorrhagic corpus luteum measuring 2.5 cm. in diameter and filled with blood clot. The wall had a yellowish irregular covering.

The lesion was reported by the pathologist as an hemorrhagic endometrial cyst, follicular cyst and corpus luteum cyst of the ovary. The appendix revealed changes of chronic inflammation.

*Course:* On November 8, the patient suddenly went into shock. Atelectasis of both lower lobes, more marked on the right side was noted. The shock was combated with blood transfusion and the atelectasis by inhalation of 95 per cent carbon dioxide with 5 per cent oxygen.

At this time there was no thought of a connection between the hemorrhagic ovarian cyst and a probable thrombocytopenic purpura hemorrhagica, since the routine blood studies (Table I) did not include a platelet count.

TABLE I  
*Routine blood examinations*

DATE	HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	POLY-MORPHO-NUCLEAR NON-SEG.	POLY-MORPHO-NUCLEAR SEG.	LYMPHO-CYTES	MONOCYTES	EOSINO-PHILES
	<i>per cent</i>	<i>million</i>		<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
11/4/41	53	3.7	7,250	6	56	32	6	
11/5/41	55	3.7	15,700	5	78	15		2
11/7/41	43	3.37	10,950	13	74	9	4	

Two months after the operation a similar mass appeared on the left side of the pelvis and rapidly increased in size until its upper limit reached the crest of the ilium. Subsequently her periods became more frequent. The mass continued to grow so that by October 9, 1942, it approximated the size of a three months gravidity. The patient bled again very profusely from December 19, 1942 to January 2, 1943. While at home she had had an attack of fever with an apparently severe anemia for which her family physician gave her a blood transfusion and sulfonamide therapy. On January 15, 1943, she reported that she was flowing profusely after a cessation of three days following her last irregular bleeding. In view of the menometrorrhagia and the pelvic findings another laparotomy was done.

*Second Operation* (January 28, 1943). A hysterectomy and left salpingo-oophorectomy was performed through a paramedian incision to the left of the old scar. The sigmoid was found adherent intimately to the large bluish shimmering tubo-ovarian mass. There were a number of pendulous flaccid cystic dark hemorrhagic masses along its periphery; the cecum was firmly adherent to the right angle of the uterus; the uterus was partly embedded by the adherent bladder and adhesions between its postero-superior surface and the mass. The adhesions were divided by sharp and blunt dissection and several of the smaller hemorrhagic cysts were broken into and emptied by aspiration; the large portion of the tumor mass seemed to be intraligamentous and it was possible to dissect it out in large part subperitoneally. The floor of the pelvis was almost completely denuded; there was considerable oozing from denuded areas which was controlled by clamp ligatures and by hemostatic sutures. The uterus was amputated at the level of the internal os, the cervix split posteriorly and an iodoform gauze drain was passed through it into the vagina leaving ample gauze for drainage. Another Penrose gauze tubing was packed fairly tightly into the central portion of the pelvic wound to control oozing and led out of the abdominal wall. Extra-

peritonealization was accomplished by interrupted sutures taking in the serosa of the sigmoid and cecal wall including the appendices epiploica. The omentum which was found adherent and separated had to be ligated. It was rather thin and strand-like. The hemostasis was satisfactory. This was followed by typical abdominal wound closure leaving two silk threads for subcutaneous drainage. A heavy sandbag was placed over the abdominal wall for 24 hours.

The removed specimen consisted of a uterus and right adnexa. The uterus was small and globular. The posterior surface showed adhesions. The endometrial cavity measures about 4.5 cm. in height. The wall was about 2 cm. thick; the endometrium was 3.4 mm. thick. The wall had an even tan color, and multiple sections through the wall showed small opaque areas, but not containing brown fluid. The thickened endometrium was somewhat brownish discolored, especially on its surface. The attached ovarian mass measured approximately 10 x 9 x 5.5 cm. The posterior surface was flat, white, firm tissue covered by hemorrhage. Anteriorly the ovary presented a cystic appearance with a predominantly brown color. Some of the cysts had been torn, and hemorrhagic material was present on the surface. Along the upper line of the ovarian mass the tube was found to lie bound down and covered by adhesions. The fimbriated end was completely inverted and closed. In its middle extent the wall was thickened, the tube widened, being about 5.2 cm. in circumference. The lumen was also widened here. On opening the cystic loculi, most of them were found to be filled with clotted friable material. The walls of the cystic dilatations were generally smooth, discolored brown. In some areas there was adherent yellowish-brown, friable material.

The pathologist's report was as follows: Old hemorrhagic cyst of ovary, probably endometrial, however, cyst wall consisting of inflamed fibrous tissue; no endometrial tissue; chronic salpingitis.

*Course:* The clinical pathological impression was that of chocolate endometrial cysts. However, no endometrial tissue was demonstrated in the left ovarian cyst.<sup>1</sup> This fact and the massive hemorrhage and great vascularity encountered during the second operation suggested a possible connection between this condition and a primary disorder of the hemato-poietic system, more specifically thrombocytopenic purpura hemorrhagica. With this in mind I asked Dr. Peter Vogel of the hematology department of The Mount Sinai Hospital to make special examinations of the blood. His studies revealed the following: (January 29, 1943) Hemoglobin, 62 per cent; red blood cells, 4,350; white blood cells, 39,000; platelets, 130,000; non-segmented neutrophils, 12 per cent; segmented neutrophils, 70 per cent; lymphocytes, 15 per cent; monocytes, 3 per cent. Bleeding time, 6 minutes; coagulation time, 10 minutes; clot retraction, present. Dr. Vogel interpreted the foregoing findings as indicative of a "mild thrombocytopenic purpura hemorrhagica."

This was the first time a platelet count was made. The reduction in the thrombocytes was regarded as mild. Since there is frequently an increase in the number of platelets following a surgical procedure it is presumable that the thrombocytopenia was actually more marked at this time.

The patient left the hospital, but returned a week later, complaining of chilliness, abdominal rigidity and pain. Bleeding from an abdominal sinus at the lower end of the scar had produced marked anemia which was combatted by a transfusion at her home. The

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<sup>1</sup> I have asked Dr. Paul Klemperer, pathologist at Mt. Sinai Hospital, to review the slides more carefully, and he reported as follows as of September 17, 1943: "In spite of many sections which we took, there was no definite epithelial lining which would have clinched the diagnosis of endometrial cyst. However, the accumulation of large macrophages and the fibrosis of the cyst wall strongly suggest that this was originally an endometrial cyst in which the characteristic structures have already been destroyed. An interesting feature of the second case is the extensive hemorrhagic condition of the ovary which shows not only hemorrhagic corpus luteum but also atretic follicles with conspicuous hemorrhage and there is also hemorrhage within the ovarian stroma. This is probably in accord with the hemorrhagic tendency which this patient showed."

bleeding from the abdominal sinus subsided but then for the first time there was bleeding from the buccal mucosa and gums typical of thrombocytopenic purpura. The blood picture at that time is outlined in Table II.

Bone marrow aspiration yielded 250,000 cells—374 megakaryocytes.

Myeloblasts.....	1.7%	Lymphocytes.....	2.7%
Myelocytes N.....	22.3%	Hematogones.....	2. %
Myelocytes E.....	1.7%	Plasma cells.....	0.7%
Non-seg. Neutrophils.....	33.3%	Erythroblasts.....	1. %
Segmented Neutrophils.....	12.2%	Normoblasts.....	21.4%
Eosinophils.....	1.0%	(Megakaryocytes.....	0.6%)

Comment: There is lack of maturation of megakaryocytes. Otherwise bone marrow findings are essentially normal.

TABLE II  
*Blood picture after clinical signs typical of thrombocytopenic purpura*

DATE	PLATELETS	RETICULO- CYTES	HEMO- GLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	POLY- MOR- PHO- NUCLEAR SEG.	POLY- MOR- PHO- NUCLEAR NON-SEG.	LYMPHO- CYTES	MONO- CYTES
		<i>per cent</i>	<i>per cent</i>	<i>million</i>		<i>per cent</i>	<i>per cent</i>		
2/22/43	140,000	4	48	3.4	26,500	73	19	7	1
2/23/43	130,000	3	45	3.25	28,000	68	12	18	2
2/25/43			53	3.23	10,000	72	9	15	1
2/26/43	130,000	3	54	3.69	10,500	61	12	6	2
(Sed. rate, 18 mm. in 53 m.; hematocrit, 3.19 per cent; bleeding time, 4 min.; coagulation time, 9 min.; clot retraction, excellent; tourniquet test, slightly plus; pinch test, neg.)									
3/ 1/43			55	2.79					
3/ 2/43	240,000	1	57	3.8	12,200	69	6	19	4
3/ 4/43			61	3.72					
3/ 8/43			64	3.78					
3/10/43	20,000	.59	75	4.4	11,250	67	8	19	5
(Prothrombin time 21 sec.; control, 21 sec.; index, 100)									
3/12/43			70	4.0					
3/15/43			70	4.13					
3/16/43	20,000	5	78	4.8	11,400	57	4	34	5
4/12/43	40,000		76	4.44	10,250	49	10	33	5
(Eosinophiles, 2 per cent; basophiles, 1 per cent; tourniquet test, positive; pinch test, positive; coagulation time, 11 minutes; clot retraction, absent; bleeding time, 12 minutes; clotting time, 12 minutes).									

The blood findings were now considered those of a chronic purpura hemorrhagica. The patient was to be kept under observation for a few months to follow the trend of the blood picture bearing in mind the possible indication for splenectomy.

Follow-up examination of the blood (June 27, 1943) revealed the following: Hemoglobin, 80 per cent; red blood cells, 4,900,000; white blood cells, 7,600; platelets, 15,000; reticulocytes, 0.5 per cent; non-segmented neutrophils, 4 per cent; segmented neutrophils, 70 per cent; eosinophils, 2 per cent; lymphocytes, 20 per cent; monocytes, 4 per cent. Except for a severe cythrombopenia, the blood findings were normal.

Blood examination on September 21, 1943, showed an improvement in the hemoglobin and red blood cell count; the platelets were 30,000; the coagulation time, 9 minutes; bleeding time, 6 minutes.

It is of interest to note that the spleen was at no time palpable.

When last seen on September 24, 1943 the patient's general condition was excellent.

## SUMMARY AND COMMENT

A young woman, aged 25 years, gave a history of petechiae, nose bleeds and prolonged bleeding following trauma up to two years before seeking relief from pelvic pain. Her menstrual periods were inclined to be profuse and at times prolonged. On pelvic examination a mass was found to the right of the uterus, which at laparotomy proved to be a hemorrhagic ovarian cyst. Several months later a similar mass developed on the other side. Profuse, irregular and more frequent menstruation later necessitated a second laparotomy which revealed a left-sided hemorrhagic ovarian cyst with much perio-ophoritis and perimetritis. Grossly the lesion resembled endometrial cysts. A hysterectomy was found to be necessary. During the operation excessive bleeding was encountered. The surprising absence of endometrial tissue in the microscopic examination of the left-sided ovarian cyst walls combined with the increased bleeding tendency and a severe anemia suggested the possibility of thrombocytopenic purpura of which the ovarian hemorrhage was a major manifestation. This actually proved to be the case as was established by subsequent blood examinations and by the development of typical lesions of the buccal mucosa.

The case is unique in that large hemorrhagic ovarian cysts with menometrorrhagia developed before pathognomonic evidence was adduced of an underlying purpura hemorrhagica. The characteristic picture of thrombocytopenic purpura presented itself only after the surgical procedure which was resorted to in order to arrest the uterine bleeding. Had the diagnosis of the underlying blood disease been possible earlier, splenectomy might have improved the menometrorrhagia. But whether such a measure could have induced resorption and disappearance of the hemorrhagic ovarian cysts remains a matter of speculation. The production of these cysts in the light of the bleeding tendency may be explained by increased and prolonged intrafollicular and intraovarian hemorrhage. Endometrial tissue if originally present in the left ovary may thus have been destroyed defeating microscopic detection.

## CONCLUSION

This case points to the importance of searching carefully for symptoms suggesting a possible hemorrhagic diathesis in instances of gynecologic lesions associated with menometrorrhagia in young women. Complete and thorough blood examinations are essential despite the apparent justification for pelvic surgery.

# THE EARLY YEARS AND RAPID DEVELOPMENT OF NEUROLOGY IN AMERICA AND ITS RELATION TO MEDICAL SCIENCE. I\*

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It is a very unusual privilege for a man of my age to be allowed to contribute an article to a volume in honor of a colleague several years his senior. Evidently both of us are old but not aged. We were youths together, began our medical careers at about the same age and have for many decades been devoted to this great institution and to the cause of the progress of medical science in America. Although our paths diverged slightly Doctor Meyer as internist knew of the struggles of the early neurologists and like the other great medical men of those days (with a few exceptions) was in sympathy with the honest work the neurologists had set out to do.

I could not possibly have found the time to prepare an adequate article in the short time given me. Fortunately I have been granted the privilege of quoting liberally from an article written fully three years ago which is to be published in the first number of the *Journal of the Neurological Sciences*.<sup>1</sup> Without having The Mount Sinai Hospital especially in mind, reference to it proves what an important rôle this Hospital and its medical staff played in the development of Neurology in this country and I am especially proud to recall the names of many estimable colleagues who were associated with us. Dr. Meyer and I have lived through the "Heroic" age of medicine and I hope the reader will pardon the frequent mention of the present writer's name.

It was my good fortune that my active career as neurologist and psychiatrist covered the last half century (and more) and that I may be able to pay a just tribute to the many colleagues whose work and influence should not be forgotten, especially at this very time when organic neurology and neuropsychiatry are entering upon a new and most promising era.

Due acknowledgment was made the world over in the early eighties for the work done in general medicine by Austin Flint, William Draper, E. G. Janeway, Abraham Jacobi; and in surgery by McBurney, William T. Bull, W. W. Keen, Sayre and others, not to forget the earlier achievements of McDowell and Marion Sims. The specialties were slow in gaining their full independence. Medicine was trying to keep a strangle hold on neurology; not unlike what is happening in some quarters this very day. Of course, neurology should remain

\* This is part of a paper, to be completed in a subsequent issue of this *Journal*, penned by one to whom Sir James Purves-Stewart addressed the following: "You are indeed our Nestor of Neuropsychology. All of us, friends and admirers throughout the world, esteem it a pleasure to have known you both personally and by your works. You have been the inspiration of eager disciples. We all hope you will live for many years to be an acute and chronic stimulus to your followers."—Ed.

<sup>1</sup> Some Comments on the Early Years of Neurology in America and Present Day Trends in Neuropsychiatric Research.

in closest touch with general medicine to the advantage of medicine and neurology.

In the late seventies, after four years at Harvard College, under the special guidance of William James, and because of my interest in philosophy and psychology, I determined to devote myself to diseases of the mind and to take my entire medical course abroad. Even at that time President Eliot of Harvard was credited with the remark: "It's a good thing to go abroad for study; it's still better to have been there." As an American, and while working at Strasburg (1878-1882) under Waldeyer, Goltz, von Recklinghausen, Kussmaul, Hoppe-Seyler at the University of Strasburg—in those happier days when German science was unhampered—I was constantly on the alert to note whether the work of my countrymen would be referred to. No reference was made to anyone except to Weir Mitchell and even in England, under Hughlings Jackson, reference was made to the Weir Mitchell-Playfair treatment and to nothing else of American worth. I knew by diligent reading, while abroad, how much had already been achieved by William A. Hammond, E. C. Seguin, and Spitzka in New York; Weir Mitchell, C. K. Mills, Wharton Sinkler, F. X. Dercum, James Hendrie Lloyd in Philadelphia; James J. Putnam, Robert T. Edes in Boston. The middle west loomed up with the work of Jewell and with the publication of the *Journal of Mental and Nervous Disease*. On my return to this country, I felt especially the powerful influence of Edward Constant Sequin, who deserves especial mention at my hands, his grateful pupil and assistant. From a review which I wrote of his contributions to medicine in May 1898, I quote what follows: In 1867 he wrote two short papers on subcutaneous injections of quinine in malarial neuralgia. He was associated with the famous Draper at the New York Hospital. In 1869, he went to Paris where he became a student of Brown-Séquard, Charcot and Ranvier, the master minds of the day. He returned to America at a time when only two other men were prominent in the specialty—Weir Mitchell and Hammond. In 1878 Sequin reported upon the findings in a case of cerebrospinal sclerosis—in the spinal cord only. His first article on the aphasia question brought a fine review of the arguments for and against Broca's theories. His discussion of anterior poliomyelitis helped to promote the understanding of this important disease. His lectures on cortical localization delivered at the College of Physicians and Surgeons were masterly expositions of the subject. These lectures were delivered, in great part, before Nothnagel's work appeared and helped to elucidate a subject which was then much in doubt. His most notable contribution was the recognition, in advance of Erb and Charcot, of spastic paralysis. It is well to insist upon Sequin's merits in this field, since European writers have done him scant justice. Great as a clinician, he was still greater as a therapist and showed that neurologists may achieve much in the treatment as well as in the diagnosis of nervous disorders. In 1877 he wrote a paper on the "Abuse and Use of the Bromides" which might be read to advantage by many at the present day.<sup>2</sup>

<sup>2</sup> In a letter dated *January 8, 1892* in which Adolf Struempell recognized that he and I differed (at that time) in our interpretation of infantile cerebral palsies; but both of us

In 1885 Birdsall and I were Sequin's assistants. Everyone in that clinic seemed possessed with the ambition to further our young science. The meetings<sup>3</sup> of the New York Neurological Society (founded in 1872) and of the American Neurological Association (founded in 1874) stimulated rivalry between individuals and groups of aspiring neurologists and psychiatrists.

I find that in 1882, in his Presidential address before the American Neurological Association, William A. Hammond said that nowhere in the world was Neurological Science better cultivated than in this country and he thought the Association had no reason to feel ashamed of the part it had taken in it, and he was right. In addition to those already mentioned there were Graeme Hammond (who may not remember that in 1881 he wrote on "The Hypothetical Auditory Tract in the Light of Recent Anatomical Observations," Amidon, Landon Carter Gray, William J. Morton, Beard and Rockwell; in Philadelphia with Mitchell, Mills and Sinkler, were Dereum, Lloyd, John K. Mitchell, Burr and Isaac Ott and East of us were James J. Putnam, Walton, Morton Prince, our early psychologist, E. W. Taylor, whose paper on Family Periodic Paralysis I remember well, and S. G. Webber. Soon Philip Coombs Knapp loomed up, and in Chicago, Hugh Patrick became active, writing forcibly on syringomyelia and tabes.

Our young science was at that period under the influence of Munk, Ferrier, Fritsch and Hitzig and cerebral localization was the all absorbing topic of the day. Soon spinal localization was almost equally stirring, involving not only the determination of the level of disease, but the spinal tracts involved. All of us were well grounded in the anatomy, physiology and pathology of the structures involved, and on this safe basis, research was begun and continued for many years thereafter. While Seguin wrote brilliantly, as he always did, on arsenical myelitis, Mills studied, in his careful manner, twelve cases of brain tumor with reference to diagnosis; and to prove that at that early day, accurate scientific work was in vogue, Amidon (1882, mind you) discussed *myography* of nerve degeneration in animals and man. At this time the elder Hammond's and Graeme Hammond's writings on athetosis received universal acclaim, and the American group recognized their debt to European investigators by electing as the first Honorary Members of the American Neurological Association, Charcot, Erb, Hughlings Jackson, Meynert, Westphal, and as Associate Honorary Members, Ferrier, Gowers, Golgi, and Obersteiner. The Americans had the great

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realized that there was a distinct difference between infantile and adult cerebral palsies. Struempell deserves credit for his boldness in believing as Pierre Marie did in the identity of cerebral and infantile cerebral palsies. Struempell goes on to say, "Whether we (he and I) are right or wrong, we are seekers after truth", and he winds up the friendliest sort of letter with the remark, "so much and thorough work is being done in America in the domain of Neurology, that we German neurologists might learn a great deal." (1892—Mind you—Not 1943!)

<sup>3</sup> To be certain of my facts for this imperfect record, the Transactions of these two Associations have been my chief reliance, and I now feel doubly justified in having been a most regular attendant at Society meetings all these years. Parenthetically, be it said, that it is not altogether boring to read what any one of us and one's colleagues said in discussions held forty and fifty years ago.

advantage that they were not tied down to any one school and were able to accept or reject theories and doctrines according to their best judgment. Soon we Americans developed our own problems.

The Flexners have written ably of this period which William Welch flourished as the "Heroic Age of Medicine." It was during this same period that neurology in American passed from adolescence into a vigorous manhood. In 1884 I was one of the adolescents; soon thereafter I had the good fortune to be intimately associated with E. C. Seguin and in a few months began to realize that his painstaking clinical examinations meant more to me and revealed more than all the previous drilling in foreign clinics, inspiring and useful as that had been. As I try to recall those adolescent days, Charles L. Dana, M. Allen Starr, Amidon, Birdsall, Landon Carter Gray, George W. Jacoby, Frederick Peterson stand out most prominently. Very soon E. D. Fisher, Joseph Collins, Pearce Bailey, Ramsay Hunt, Joseph Fraenkel were added to this group. I may refer to individual contributions later on; let me remind the present day student that at that period (the last quarter of the last century) medical science was under the influence of Virchow, DuBois Reymond, Charcot, Hughlings Jackson. A thorough knowledge of the structure and function of all the organs and of the changes caused by disease was the basis of all research. No one could claim to be a medical scientist unless he had a thorough acquaintance with pathology and above all, with histologic changes due to disease.

The conception of disease may have been hampered by this purely anatomical and pathological point of view; but it helped us to establish carefully definite types of disease. Even at this day, when we are tempted to think of disease with reference to causation, owing to our evergrowing knowledge of bacteriology and allied fields, let us be grateful for these former basic studies; the establishment of very definite types was a real boon. If we had not very definitely described and circumscribed anterior poliomyelitis, what an indiscriminate group of diseases would have been included under infantile spinal paralysis, acute encephalomyelitis and what not. As it is I have the suspicion that we might have done better with disseminated sclerosis and amyotrophic lateral sclerosis, under which heterogeneous forms of disease, rather than definite types of disease have often been included.

At all events, there was, in those early days, a very sincere effort to provide a safe foundation for further research. To those who may be inclined to have a slight sneer for the clinician and think him inferior to the laboratory worker, let me say, as I have said elsewhere, *all true scientific research in medicine stems from the bedside*. The patient presents the problem, it is for the physician to study and solve it; and he can do much toward formulating these problems if he will wear his thinking cap at the bedside.

The causation of disease and the relation of one form to another began to be of paramount importance. Mills in the early eighties, spoke before the American Neurological Association of locomotor ataxia terminating as general paralysis of the insane, doubting any direct causal relation between the two, participating in the world wide debate, lasting a full decade, on the specific origin of tabes and

general paralysis. Charcot's insistence that disseminated sclerosis can exhibit all the symptoms of general paralysis of the insane, bolstered Mills' contention at the time, and although it soon lost its force, it led to intensive study on all sides of the relation of these conditions to one another, inducing Birdsall and others to undertake careful histologic studies and helped to clarify the understanding of specific diseases of the nervous system in which, during this decade, several of us now older men took an active part.

In reviewing the literature of the past sixty years, a deep impression was left of the almost unconscious rôle every honest scientific worker plays in the development of his special branch of medicine. That much time was given to discussion of the treatment of locomotor ataxia by nitrate of silver, galvanism, hydrotherapy, prolonged rest, may mean little to us today, but at this same time Spitzka was holding forth on the alleged relation of speech disturbances, of the patella tendon reflex in parietic dementia, all preparatory to the final evaluation of the part syphilis plays; and by the way, Spitzka, as the foremost and surely the most scholarly psychiatrist of that era, was proud of neurology and of its fundamental importance in psychiatry; he was proud of being a thorough brain anatomist; a close friend of Burt G. Wilder, a follower of Meynert and of Westphal. In those same years, Amidon discussed tetanoid paraplegia and Parkinson's disease without tremor, always the effort to establish well pronounced types. At that distant day, the progressive muscular atrophies, under the stimulation of Erb's writings, aroused great interest.

Virgil P. Gibney, as orthopedist, was closely linked with the neurologists in the special studies. For several years the careful differentiation between the truly spinal and other forms of progressive muscular wasting held the center of the stage and to this day that line of research is of great value.

To the senior group of American neurologists, a younger group was added in the years 1882-1888. Most of them had some training abroad.<sup>4</sup> We were proud of those who had preceded us, eager to follow in their footsteps and to help put American neurology in the forefront of the scientific battle. As I recall those early days, I feel the thrill of the warm welcome accorded us youngsters by Weir Mitchell, Mills, Seguin, Landon Carter Gray and Spitzka. It will be difficult to remain entirely impersonal from this time on, but let me indicate in a general way the subjects that busied us most and to which each, in his way, tried to contribute his mite.

The experimental work of neurophysiologists had set the pace for kindred groups here and abroad in the verification of cerebral localization. While there was general endorsement of the principles of topical diagnosis as promulgated by Ferrier, Nothnagel, Munk, Hitzig and some others, so eminent a physiologist as Goltz allowed that there were certain functions to be ascribed to definite regions of the cortex. He was not willing to have the cortex a sort of crazy quilt; after all, the entire cortex had a part in every brain function. I had the opportunity in 1881 and 1882 to hear Goltz expound his dissenting views in his laboratory and

<sup>4</sup> Starr and the present writer met in Meynert's laboratory in 1882 and next to them sat Sigmund Freud and Gabriel Anton.

in his jovial manner. Starr and Mills deserve especial credit for their many writings including text-books, in support of the determination of special cortical (functional) areas. As authors and teachers both had great influence in their respective cities and were powerful factors in the rapid rise of neurosurgery, acknowledging the fundamental work of Hughlings Jackson, Ferrier and Horsley which they were able to amplify and multiply with the aid of W. W. Keen and Frazier, McBurney and Arpad Gerster, work that was so brilliantly performed, or at least promoted by the eminent neurosurgeons of our day—including Cushing, Dandy and many other celebrities of this later era, and who carried this branch of surgical science to unexpected heights.<sup>5</sup>

It is no injustice to contemporary neurosurgeons to pay tribute to the famous surgeons of a former day who did very remarkable pioneer work in brain and spinal cord surgery. At this time I must omit detailed reference to the origin of neurosurgery, which I have discussed (briefly) elsewhere. Personally, I am especially indebted to Arpad Gerster, the great and early promulgator of aseptic surgery upon whose skill I relied in the removal of brain tumors, and the surgical treatment of focal epilepsies nearly fifty years ago. Gerster also realized to the full the value of careful neurological examination and it was largely through his influence that I was appointed the first Consulting Neurologist at The Mount Sinai Hospital, and where a few years later, the first Neurological Division in a voluntary hospital in New York City was established under my direction. I am indebted to A. A. Berg for the removal, over thirty years ago, of a tumor of the Gasserian ganglion with complete recovery and two years later Elsberg joined me in discussing neurosurgical work with reference to spinal cord lesions. It is a matter of historical justice to give the general surgeon credit for the beginning of neurosurgery without detracting from the fame of those whose skill is still the talk of the present day medical world. Let me emphasize once more that in the long drawn out discussions on cerebral functions and cerebral localization, and in the development of neurosurgical procedures, neurology in America played a very significant rôle.

*(To be continued)*

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<sup>5</sup> I wonder how many of our present day colleagues know that in 1901 W. B. Cannon wrote an interesting article on cerebral pressure following trauma (Am. J. Physiol. October 1, 1901).

# SPONTANEOUS PNEUMOTHORAX

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Pneumothorax is a condition in which air, or any other gas, is present in the pleural cavity. The most prominent organ in the chest that comes to mind when considering spontaneous rupture, is the lung; and when this organ ruptures, a pneumothorax results. Infrequently, a spontaneous pneumothorax occurs at the mediastinum, with the resulting most prominent symptoms being pain behind the sternum and in the neck. On physical examination, there is the highly diagnostic "egg-shell" crackle in the neck. It is conceivable that a high tension pneumothorax in the region of the mediastinum may rupture into the contralateral hemithorax and thus bring about a bilateral pneumothorax. However, a spontaneous mediastinal pneumothorax is uncommon; the traumatic mediastinal pneumothorax these days is not, thanks to the ubiquitous automobile. It is possible for air present in the esophagus or in a large bronchus, due to trauma, suppurative or neoplastic disease, to find its way into the pleural cavity; and also for extrapulmonary lesions such as subphrenic abscess or a perforated peptic ulcer, to permit air to enter from below the diaphragm into the pleural space. In rare instances, caries of the ribs or sternum may be the underlying cause for this condition. Thus pneumothorax may be classified as:

1. Traumatic
2. Artificial
3. Spontaneous, due to pulmonary tuberculosis, neoplasm, suppuration, abscess, gangrene, mycotic disease, bronchiectasis, infection, emphysema, asthma, pneumoconiosis, pneumonia, foreign body and pulmonary cysts.
4. Spontaneous complicating artificial pneumothorax.
5. Spontaneous idiopathic.

The most common cause of spontaneous pneumothorax is pulmonary tuberculosis. Biach (1) found 918 cases of spontaneous pneumothorax in Vienna hospitals due to the following conditions:

Pulmonary tuberculosis.....	715
Gangrene of the lung.....	65
Empyema.....	45
Wounds of the chest.....	32
Bronchiectasis.....	10
Abscess of lung.....	10
Emphysema.....	7
Hemorrhagic infarct.....	4
Chest puncture.....	3
Hydatid disease of the lung.....	1
Rupture of a bronchial gland into bronchus and pleura.....	1
Caries of the rib.....	1
Caries of the sternum.....	1
Abscess of breast.....	1
Perforation of esophagus.....	2
Gastric ulcer into pleura.....	1
Sacculated peritoneal abscess into pleura.....	1
Undetermined causes.....	16

Aside from its etiology, pneumothorax may be further designated as *external*, such as occurs after pleural tapping or an injury from without; *internal*, as after rupture of the lung from within. *Open*, when the opening is patent in inspiration and expiration; and *closed*, when the opening is closed in inspiration and expiration. When it is patent in inspiration and closed in expiration, the term *valvular* pneumothorax is applied.

A pneumothorax may also be *unilateral*, *solitary* or *bilateral simultaneous* or *bilateral alternating*. The traumatic variety, direct or indirect, of surgical or non-surgical origin, need not be considered here. In many of the spontaneous cases, a traumatic element may be present, so that it is occasionally difficult to draw a sharp line of distinction between the traumatic and spontaneous varieties.

Artificial pneumothorax, one of the most important aids in the modern treatment of tuberculosis, will not be discussed at length here, but will be referred to as occasion requires.

The spontaneous form of pneumothorax occurring in tuberculosis averages about four times greater in frequency in the male than in the female, although tuberculosis is found about twice as often in the male as in the female. In the idiopathic variety, strangely enough, it occurs mostly in the male. One may see ten or more cases in the male for every one in the female. In tuberculosis, although pneumothorax may occur early in the disease, it usually does so in the moderately advanced and advanced stages. The further along the disease, the greater is the possibility of a complicating pleural effusion in the wake of a spontaneous pneumothorax. In the advanced form, the effusion is apt to become purulent and form a serious complication. Most patients who develop tubercular empyema do not recover, but thanks to the modern progress of surgery, and the better understanding of the indications for surgery and the time for intervention, more hope is held out that more and more of these patients may be brought back to comparative good health.

When a caseating tubercle is the cause of the effusion, the fluid may be serous, tubercle bacilli will be recovered frequently, and the fluid seldom turns to pus. On the other hand, when a bronchial fistula is the cause in the course of caseation, pus is almost always the rule with tubercle bacilli or mixed infection present in the fluid. The problem presented by these cases consists in evacuating the pus promptly and closing the fistula. Several types of treatment have been devised. When mixed infection is present, the condition is always serious and death ensues unless energetic measures are instituted promptly. Thoracotomy to drain the pus, to be followed soon thereafter by thoracoplasty, is the treatment of choice. Thoracotomy alone, though it may relieve the immediate symptoms, unless followed up by thoracoplasty, frequently does not prevent a fatal issue.

A pneumothorax may occur in tuberculosis without the development of fluid. The pneumothorax may be complete and show no adhesions, but usually the lung does not collapse completely, and on x-ray examination the lung is found bound down by one or several adhesions attached to any part of the chest wall, most frequently in the apical region. When one views an x-ray film of a spontaneous pneumothorax, showing one or more adhesions, one must suspect tuberculosis as the underlying cause, and tuberculosis must be excluded also as the etiologic

factor when an effusion complicates the situation. The idiopathic spontaneous case, too, may develop fluid, but in this variety fluid is the exception rather than the rule. This type of patient is usually free from fever even with a little fluid. When there is considerable fluid and fever, the suspicion of tuberculosis must be strongly entertained. The fluid in the idiopathic form contains very few cells, but if many lymphocytes are present, tuberculosis is to be strongly suspected. If tubercle bacilli are present, a caseating area in the pleura is likely to be present. If pus is present, a bronchial fistula or rupture of a cavity is the probable cause.

In the spontaneous form, due to pulmonary disease; in the artificial variety with fluid, or without fluid when the pleura thickens after years of treatment, the pleural leaves usually adhere when the lung re-expands. The experienced physician knows how difficult it is to fully recollapse a lung of the artificial type after pneumothorax has been abandoned, especially when fluid has been present during the previous course of treatment. In the idiopathic variety, the leaves usually do not adhere and this explains why in this type, pneumothorax can recur repeatedly on the same side.

When blood is found in the pleural cavity in the absence of trauma, a neoplasm is to be suspected. Occasionally it occurs in tuberculosis and sometimes in the idiopathic variety due to a rupture of a vessel by the tearing of an adhesion. Blood in the pleural space is always a grave finding. It may be very profuse and extensive, causing exsanguination and death. It may be so extensive as to dislocate the mediastinum, heart and large vessels, causing danger to life; or it may be slight and moderate in amount and at the most require aspiration. Repeated rapid reaccumulation is almost always the rule in neoplasm, and although it may recur in tuberculosis, it never reaccumulates as rapidly or extensively as it does in neoplasm. It may require thoracoscopy to localize and cauterize the bleeding point, or an open operation to tie off the bleeding vessel; or it may end in empyema, necessitating surgical interference, resection of ribs or partial or complete thoracoplasty. Hemorrhage into the pleura must always be treated promptly and with great care. It leads to death, either alone or as a result of complications in from 37 to 50 per cent of the cases.

Spontaneous pneumothorax may occur in the newborn, as after insufflation with a catheter to bring on respiration. DeCosta (2), in April 1940, described two cases of his own, considered a rare occurrence, and could find reference to only sixty-seven cases in the literature. One of his cases was so affected that he developed subcutaneous emphysema and pneumoperitoneum. It may occur after surgical operations on the abdomen following intratracheal anesthesia (3). The warning here is to watch the pressure.

Some years ago I saw a patient, who, following obstetric delivery (4), developed chest pain and marked shortness of breath. A diagnosis of atelectasis had been made, but owing to the pain which is absent in atelectasis, displacement of the heart to the contralateral side, which is the reverse in atelectasis, and marked hyperresonance as against dullness in atelectasis, a diagnosis of spontaneous pneumothorax was made, later confirmed by x-ray.

Many years ago I saw an infant, six weeks old, in whom a diagnosis of pneu-

monia had been made, develop a spontaneous pneumothorax, and subsequent x-ray examination revealed, in addition to this finding an abscess of the lung in the consolidated area.

Sokoloff (5) described a series of cases of spontaneous pneumothorax occurring in silico-anthraco-sis. Most of these patients showed the usual adhesions common in pneumoconiosis. Several were bilateral cases, all of whom died. Of those cases that were complicated by tuberculosis, almost all died. Of seven or eight cases in which tuberculosis was absent, only one died.

Bachmann (6) described a familial type of pneumothorax. He relates the case of a father and daughter, both of whom showed the recurrent type of disease.

Bottero (7) described this condition of pneumothorax as peculiar in asthmatic families, and states that the cause is a congenital one due to deficiency in pulmonary resistance.

#### HISTORICAL NOTE

Hippocrates, though he noted the succussion splash, succeeded in diagnosing fluid and empyema, yet failed to distinguish between fluid and air. The possibility of uncomplicated air in the pleural space was never realized by this keen observer who laid the groundwork for our present day knowledge of pulmonary tuberculosis.

Hewson (1739-1774) was the first observer to note the presence of air in the pleural cavity. Itard (8), in 1803, was the first to describe pneumothorax in the apparently healthy, a group now classified as idiopathic spontaneous pneumothorax.

Laennec (9) in his book on Diseases of the Lungs and Heart (1819) described the signs and symptoms of pneumothorax in tuberculosis so fully, that little has been added since then.

#### SYMPTOMS OF SPONTANEOUS PNEUMOTHORAX

The onset of spontaneous pneumothorax in the average case is acute. The symptoms depend upon the rate, amount and rapidity of the flow of air which enters the pleural space. The patient complains of sharp pain, in one or the other side or front of the chest, radiating to the back, sometimes up into the neck, sometimes down into the abdomen, occasionally down the arm, and sometimes completely across from one side to the other. The average case as seen in practice is frequently mistakenly diagnosed "acute pleurisy." In a severe case, the pain is unusually sharp, and for this reason this condition may be confused with other diseases. As a rule cough is present, but this is usually dry. Sputum is absent when the pleura alone is involved. The cough is transient, short, hacking in character and painful. When fluid is present, with dullness at the base, it may be mistaken for pneumonia. With the pain localized in the upper portion of the abdomen, it can be mistaken for "ruptured peptic ulcer," "acute gall bladder," "nephrolithiasis," "acute pancreatitis," "ruptured appendix," "rupture of the large gut." When the pain was referred to the left arm in left-sided cases, angina and even coronary thrombosis have been diagnosed. A. M. Master

has recently called attention to a series of cases of spontaneous pneumothorax wrongly diagnosed as heart disease. In this series the electrocardiographic tracings showed some lowering of the voltage and inversion of the T wave in the lead III. These findings he attributes not only to the marked displacement of the heart, but to torsion of the heart, to impingement on the large vessels and poor filling of the right heart.

The pain may be so severe as to cause collapse of the patient with loss of consciousness. In the average case the pain is severe or moderately severe, usually confined to the region of the chest alone and associated with dyspnea. In some cases the pain may be so slight and fleeting in character as to escape attention altogether, and may be considered muscular or neuralgic in character, and not until the dyspnea becomes distressing does the patient seek medical help.

Some years ago I saw a patient who stated that while at work, he developed some shortness of breath which disturbed him not at all and he definitely suffered no pain. He continued working until the end of the day, in the evening he visited a friend and then noticed that his dyspnea became troublesome; it steadily grew worse so that during the night he had to summon a doctor. The following morning an x-ray film revealed a complete collapse of a lung. Neither at the onset nor throughout his illness did he ever complain of any pain. This case is of interest, not alone for the absence of pain, but is illustrative of the gradual effect of a ball-valve or valvular pneumothorax. In the classical textbook case the lung collapses promptly and completely, as a toy balloon pricked with a pin; but in practice such an event is more the exception than the rule.

The dyspnea is directly proportionate to the degree of lung collapse. When there is little dyspnea, there is little collapse; when there is marked dyspnea, there is considerable collapse, and this will increase if the mediastinum is pushed over to the contralateral side interfering with the function of the good lung and with the circulation of the blood.

When pain is present, it lasts usually from a few hours to a few days. In a tension pneumothorax with valvular action, when air enters the pleural cavity and little escapes, the dyspnea may become very serious, threaten life, and must receive prompt treatment.

In cases where an open fistula is present, a gas analysis is helpful in differentiating between a closed pneumothorax and an open one. It is well known that when air enters the pleural cavity, the nitrogen fraction remains constant, but the oxygen is absorbed quickly by the tissues and replaced by carbon-dioxide. A gas analysis showing the constant presence of a large amount of oxygen is indicative of a pulmonary fistula.

In most cases of idiopathic pneumothorax, a large degree of collapse is the rule. In the tubercular patient with spontaneous pneumothorax, adhesions are usually present, which vary in size, location and tension with the stage of disease. Cyanosis is never present in the idiopathic type unless there is interference with blood circulation. It is present and becomes serious in cases of chronic bronchitis and emphysema, or in cases complicated by chronic heart disease. In such cases the outlook for life is always very poor. In rare instances a spon-

taneous pneumothorax in tuberculosis may be followed by a pneumopericardium with the usual complication of fluid, resulting in hydropneumothorax and hydro-pneumopericardium which usually go on to pyopneumothorax and pyopneumopericardium. Succussion is diagnostic of the pleural effusion. The metallic splash heard over the body of the heart, synchronous with every beat, is characteristic of air and fluid in the pericardial cavity and once heard is never forgotten. Dr. Alfred Meyer may recollect an instance of this complication which I sent into his service many years ago from the Tuberculosis Clinic.

Bilateral spontaneous pneumothorax in chronic pulmonary emphysema carries a mortality of almost one hundred per cent. In the bilateral idiopathic variety the mortality is about 50 per cent because these people are usually young, and being free from organic pulmonary or cardiac disease there is less cyanosis and no involvement of the right heart. Bilateral therapeutic or artificial pneumothorax in tuberculosis, when complicated by a spontaneous pneumothorax, more often than not has a fatal issue.

The dyspnea of the idiopathic type is accompanied by pallor; in extreme cases only, by cyanosis, shock and complete loss of consciousness. Air hunger may be present, a true anoxemia due to the sudden loss of function of the collapsed lung, suddenly creating an immense task for the functioning other lung and the right heart to satisfy the urgent need for oxygen. If there occurs a complicating marked displacement of the heart and large vessels, the ensuing burden becomes tremendous. Not enough oxygen reaches the cardio-respiratory centers in the brain, which stimulated by the carbon-dioxide sends out a hurry call resulting in more rapid breathing and faster heart action.

In the idiopathic variety, fever is absent. When fever is present, inflammatory disease must be suspected. The complications of spontaneous pneumothorax in general depend upon the underlying disease and cannot be discussed here.

#### PHYSICAL SIGNS OF PNEUMOTHORAX

Like the symptoms, the physical signs of pneumothorax vary a great deal, and more frequently lack the clear textbook pattern. Physical signs may be absent altogether and the diagnosis missed unless an x-ray examination is made. The fluoroscope will assist in diagnosing most cases but on occasion the fluoroscope will fail. A small apical pneumothorax, a marginal one, one with a very thin visceral pleura, may be missed in the fluoroscope but will be disclosed by x-ray film.

Attention may be directed to a few of the important physical signs: appearance of the patient, his color, his upright position in bed, his dyspnea, lack of movement of the affected side, are important; diminished breathing on the affected side, its amphoric quality heard only in a large pneumothorax, helps in the diagnosis; the coin sound is helpful when present. In the presence of a fistula with fluid, a water whistle sound may be heard. This is produced by bubbles of air passing through the fluid. In my experience the most important single sign is an amphoric quality to the whisper heard best with the naked ear. In

the light of a history of sudden pain with shortness of breath, this physical finding is quite diagnostic.

#### DIFFERENTIAL DIAGNOSIS

1. Large pulmonary cavity
2. Subphrenic pyopneumothorax
3. Diaphragmatic hernia
4. Gaseous distension of the stomach
5. Pleurisy with effusion
6. Eventration of the diaphragm with stomach displaced upward
7. Congenital cyst
8. Herniation of the stomach into the chest cavity resembling a collection of fluid with air.

The many and various points of differentiation between all the aforementioned conditions cannot be discussed in great detail here, but a word or two of caution may be offered as to the last condition. Succussion is present in this condition as in hydropneumothorax. Aspiration will yield stomach contents. This procedure should be avoided, however, since it may prove dangerous. When in doubt, one should always look for the edge of the diaphragm and if this is indistinct, a stomach tube should be passed down the esophagus with the patient placed behind the fluoroscopic screen. This examination can be confirmed by a barium meal and in this way error can be avoided.

As has been indicated, spontaneous pneumothorax may complicate many pulmonary disorders. For years, tuberculosis has been accepted as the most common cause. Many authors state that about 80 per cent of all spontaneous pneumothoraces are due to tuberculosis. Brief mention may be made as to the manner in which spontaneous pneumothorax eventuates in cases of tuberculosis. It is believed that when a caseating tubercle on the surface of the pleura softens and ruptures, air is permitted to travel from the lung into the pleural space. When a subpleural tubercle blocks a terminal bronchus, the air vesicle distal to it enlarges and on rupture, air enters the pleural space. When a caseating tubercle discharges its contents into the pleural space, an infection is set up, fluid forms and tubercle bacilli may be recovered from the fluid. In time the fluid may become purulent resulting in a pyopneumothorax. I have seen many instances of tubercles on the pleura and on the surface of adhesions in the course of pneumolysis, yet no fluid resulted. The mere presence of tubercles on the surface of the pleura does not necessarily mean resulting effusion or rupture of the lung. Such tubercles may persist for a long time with impunity.

It used to be the rule for these patients, that even in the absence of demonstrable tuberculosis, following a spontaneous pneumothorax, to remain under observation for at least ten years for fear that many would develop tuberculosis, thereby proving its basis.

In more recent years, this concept of the relation between spontaneous pneumothorax and tuberculosis has changed considerably. While one cannot deny that tuberculosis is the chief cause of pneumothorax, one is impressed by the

large number of cases of pneumothorax who fail to give a preceding history of illness or disclose any evidence of tuberculosis after a meticulous examination. It is observed also that patients with tuberculosis do not develop this complication as frequently as they did since the advent of artificial pneumothorax so extensively used today and since the application of other forms of surgery. Medical and surgical interference before these patients reach the stage when spontaneous pneumothorax usually occurs, is probably the reason for the drop in numbers.

In more recent years, many cases of pneumothorax have presented themselves in whom all evidence of tuberculosis is absent, in whom even a Mantoux test is negative—the so-called idiopathic spontaneous pneumothorax. In my opinion a careful analysis of a given series of pneumothorax cases occurring at a given time in New York City, for example, would show that a large number have no relation to tuberculosis and could be classified as idiopathic.

#### IDIOPATHIC SPONTANEOUS PNEUMOTHORAX

This has been referred to as the pneumothorax of "healthy" individuals. This is a distinct clinical entity and bears no relation to any of the known diseases of the lung. Many cases are missed because one fails to bear that in mind. Whether it is increasing in frequency or whether the diagnosis is made more frequently because of the greater use of the x-ray, probably finds its answer in the more extensive use of the x-ray. It occurs mostly in tall, thin males, and mostly in the age group of twenty to thirty years. The prognosis in these cases is invariably good except in hemothorax, bilateral pneumothorax, tension, and chronic pneumothorax.

The first case of idiopathic pneumothorax was described by Itard in 1803. A great impetus to the study of this form was given by Kjaergard (10, 11), who published his first paper in 1932. This report, consisting of over ninety cases, is the most exhaustive one in the literature. He found also that most of these cases usually recover. He was fortunate in the opportunity to study six cases at autopsy, and in three found rupture of superficial air vesicles which he attributed to congenital cysts; in the other three, air vesicles had formed due to scarring. In 1933 he reported two additional cases in elderly persons, and autopsies showed rupture of congenital cysts.

Perry and Wilson (12), who also have written extensively on this subject, have agreed with this explanation. If this be so, the question arises, why does it occur almost exclusively in tall, thin males. For this observation no satisfactory explanation apparently has yet been offered. In this group it may be so silent as to produce no symptoms. Wilson reports five cases with no symptoms in students at Yale University in four years as a result of routine x-ray examinations. "Silent cases" have been reported at autopsies. Such cases obviously are missed without an x-ray examination. The French investigators also have observed that young males are susceptible to this condition, so they have referred to it as "the pneumothorax of conscripts."

Norris (13), of the Eastman Kodak Company, in April 1940, reported twenty-

five cases, of which one was a female; two-thirds were under weight. He did tuberculin tests on fifteen, and seven were negative.

Blackford (14) reported fifteen cases in a student body of twenty-five hundred students at the University of Virginia in 1939. Eleven of these occurred in the last five years, a ratio of about one in a thousand. He reported three of his cases as having occurred in 1) sleep, 2) studying and 3) waiting for a bus.

Pneumothorax in these cases occurs on the slightest exertion, viz, coughing, straining at stool, coitus, laughing, talking, sneezing and running.

One author writes, "It occurs in young people who rarely show emphysema, and spares the aged in whom emphysema is fairly common."

Kjaergard has labeled this condition "pneumothorax simplex." The accepted term today is idiopathic spontaneous pneumothorax. Some refer to it as "benign spontaneous"; some call it pneumothorax in the "apparently healthy."

Kjaergard has classified the various types of "pneumothorax simplex" in two categories: (a) anatomical, (b) clinical.

*Group A Anatomical.*

1. Partial
2. Coat-formed
3. Total pneumothorax without displacement
4. Total pneumothorax with displacement
5. Tension pneumothorax

*Group B Clinical.*

1. Chronic pneumothorax
2. Hemopneumothorax
3. Recurrent pneumothorax
4. Alternating pneumothorax
5. Bilateral pneumothorax

In twenty years time, Kjaergard was able to collect fifty-one cases, considered the condition unusual, and frankly stated that he observed an increase in the number of cases in the last five year period of the entire twenty year period.

Perry saw eighty-five cases in a fourteen year period in London, twenty-six in the first seven year period and fifty-nine in the second seven year period.

It is my impression that its increase is only apparent; that the greater frequency of the diagnosis is due to the more liberal use of the x-ray as a diagnostic medium, displacing physical diagnosis from the exalted position it once occupied.

#### RECURRENCES OF SPONTANEOUS PNEUMOTHORAX

Recurrences may be frequent on one side or the other. Castex and Mazzio (15) described eleven recurrences in one case and fourteen in another. Most cases occur on the left side and the reason for this is not clear. An attempt has been made to associate it in some manner with the location of the heart on that side.

The majority of patients suffer only one attack, following which many do laborious work for years with no recurrence. Recurrences, when they do take place, usually appear early. I saw a young man with three attacks within a

period of about six months, who re-expanded the affected lung completely in the intervals. I recollect the case of a man in his forties, a retail merchant, who presented himself with alternating pneumothoraces once a year for a total of three within two years. The exciting cause in this case in every instance was reaching for a box on a shelf.

It is advisable, following recovery, not to permit these patients to do any heavy lifting or laborious work for the first year.

Today, most authorities agree that this form of idiopathic pneumothorax and tuberculosis are unrelated, and moreover that it does not lead to tuberculosis in later years. Obviously every case in which a diagnosis of idiopathic pneumothorax has been made, should be studied carefully after complete re-expansion of the lung in order to exclude a possible tuberculosis. This study should include a careful and complete physical examination, sputum concentration examination, gavage, Mantoux test, and if possible bronchoscopic drainage to obtain specimens for culture and inoculation into animals. Obviously if the Mantoux test is definitely negative, such undue precautions are unnecessary.

Legget, Myers, and Levine (16) published a series of cases in which 50 per cent were negative to tuberculin, confirming Norris' findings.

Kjaergard found only one case of tuberculosis in a follow-up of forty-nine after a two year period.

Perry was able to re-examine fifty-five out of eighty-five cases and found no tuberculosis in his series, and he states that out of a study of two hundred and fifty cases in the literature that were followed up a number of years, only six developed tuberculosis. My own impression in this matter is that when tuberculosis is absent at the time this diagnosis is definitely established, the danger of developing tuberculosis later is no greater than exists in the average individual.

#### USE OF THE X-RAY

From the foregoing it is evident that the x-ray is the most important single method of diagnosis, and that a final diagnosis cannot be accepted without thorough x-ray studies. Without x-ray studies many of these cases, especially the "silent" ones would be missed. The x-ray examination is also useful in establishing a correct idea of the anatomical structures inside the chest and in order to form a rational basis for treatment. Fluoroscopy alone is insufficient as has been indicated before. In addition it may overlook a small mediastinal pneumothorax. Where doubt is present with ordinary x-ray films, special apical films should be made. In addition where doubt exists with a film made on ordinary inspiration, a special one should be made on forced expiration. Occasionally a lateral film is very helpful. A small pneumothorax in the postero-anterior view may resemble a congenital cyst, bullous emphysema or pneumatocele. Even the x-ray has its limitations. In a recent case of artificial pneumothorax in my hospital service, the x-ray revealed very little air despite the administration of rather large amounts. The explanation for this phenomenon was not clear at the time. This patient subsequently succumbed to his extensive pulmonary tuberculosis and an autopsy revealed an excellent

collapse, but the entire lung was plastered up against the posterior chest wall throughout its width and the entire pneumothorax lay in front of the lung. A lateral x-ray plate would have shown a very efficient pneumothorax lying anterior to the lung instead of the small amount of air that was visualized at the periphery in the axillary portion of the chest.

Some observers have attempted to explain the location of the tear in the lung as residing in the anterior portion because the back of the lung moves very little as compared to the front of the lung. Localizing the tear, short of a thoracoscopic examination, is difficult with our present methods. It has been claimed that the scar formed by the tear could be visualized in the film. I have never been able to confirm this observation.

#### TREATMENT

The average case does very well on bed rest alone for a few weeks and requires no medication other than sedation for a short time. Morphine is used when the pain is extreme. The average duration of the pneumothorax in uncomplicated cases varies from four to six weeks. Obviously it will depend in a large measure upon the completeness of the collapse and upon the presence or absence of fluid in larger or lesser amounts. The treatment in a complicated case will depend upon the underlying disease and the nature of the complications, if not idiopathic. Recurrence cannot be prevented short of establishing a symphysis of the pleural leaves with sclerosing fluids, such as plain mineral oil (17), dextrose solution 30 per cent to 50 per cent (19), Gomenol, sodium chloride or cod liver oil. Recurrences cannot be foretold in advance.

#### SPECIAL FORMS OF PNEUMOTHORAX

1. Tension pneumothorax;
2. Bilateral pneumothorax;
3. Chronic pneumothorax.

When the tension pneumothorax is complete, the fluoroscopic examination will show a paradoxical diaphragm owing to displacement of the mediastinum. The good side will move down on inspiration but the affected side will move in the reverse direction, and conversely on expiration the good side will move up and the diseased side will move down. In these cases air must be removed at once. Withdrawal of air from the chest in the tension and bilateral cases is effected by the insertion of a needle into the chest, kept in place with adhesive and a finger cot which has been pricked, slipped over the hub of the needle. The tiny opening in the cot will act as a ball valve, permitting air to escape on expiration and seal itself on inspiration. The case may be serious enough to aspirate promptly or more forcibly with the pneumothorax machine with the bottles reversed, or with a large hand syringe. If the condition is not too serious, rubber tubing may be attached to the needle under water and permit the air bubbles to escape slowly. If a vacuum is necessary, water suction may be

tried or the electric pump, but the pressure must always be such as not to injure the lung and not to interfere with the closure of the tear in the lung.

It is difficult to prognosticate when to give up hope for re-expansion in the chronic case. I have seen a chronic case persist for three or four years with no ill effects, and ultimately re-expand fully. On the other hand another case that refused to re-expand after several years was treated with sterile mineral oil and the air space was replaced by thickened pleura. This was followed by marked deformity of the chest, with flattening on the affected side, drooping of the shoulder, and some scoliosis of the spine.

Another patient with a chronic hydropneumothorax succeeded in re-expanding her lung following a phrenic crush.

Thoracoplasty has been used in some of these cases but I believe that this method should be postponed as long as possible and a conservative attitude maintained.

In the bilateral idiopathic spontaneous, in the bilateral spontaneous following emphysema or asthma, in the bilateral artificial with a complicating spontaneous when life is in danger, immediate aspiration is imperative. In these cases since the needle may have to be retained in the chest for some time, one should bear in mind the possibility of infection despite all aseptic precautions. A needle left in place too long may be followed by infection. It may be necessary to remove it from one spot to another in order to avoid infection.

#### PATHOGENESIS OF IDIOPATHIC SPONTANEOUS PNEUMOTHORAX

Most workers in this field have accepted the explanation of congenital cysts as the most likely one to explain this condition. One is led to ponder whether the frequency of congenital cysts is not somewhat exaggerated and is inclined to doubt the occurrence of a single congenital cyst in the presence of otherwise healthy lungs. Congenital cysts are usually multiple and not confined to any particular section of the lung. Moreover, one sees congenital cysts proven by x-ray that do not rupture. I am excluding for the purpose of this discussion cases of bullae or pneumatocele seen in chronic pulmonary emphysema. A likely explanation for some of these cases I believe may be found in the mechanism of the so-called primary complex or primary infection in tuberculosis. The infection of Ghon is usually subpleural, and though it may appear anywhere in the lung, it is demonstrable in the x-ray in only about one case out of five. There are probably Ghon infections or fine scars marking the seat of the primary infections in such portions of the lung that are not readily accessible to the x-ray. Can this lesion produce a narrowing of a terminal bronchiole with consequent ballooning of one or more terminal alveoli which goes on to rupture? Can this lesion produce a symphysis of the pleura—an adhesion which when put under strain by a rise in the intrapulmonary pressure may rupture and open up one or more alveoli?

Terplan (20) has shown that the infection of Ghon may exist in the absence of the usual co-existing enlargement and calcification of the regional root glands.

Furthermore the infection of Ghon may be so minute as to defy detection. He has shown also that there may be complete healing with a negative Mantoux test; therefore does the negative Mantoux test throw out the possibility of a previous infection? He has also shown that on reinfection the Mantoux test again becomes positive. He reports cases of reinfection with a fresh primary complex in persons forty and fifty years of age.

In the course of a primary infection, tubercle bacilli are liberated into the circulation and some lodge at the apex of the lung to produce scars. May not some of these scars and fine calcifications situated subpleurally produce a stenosis of a terminal bronchiole creating dilatation of the regional alveoli with their subsequent rupture? Can we speculate that as a result of a bronchiolitis in childhood, due to various organisms, stenosis of a bronchiole results, with later dilatation and rupture of an homologous alveolus? May secretion in a small bronchiole produce a ball valve mechanism, permit air to enter the alveolus but prevent its exit and thus bring about a gradual ballooning of the alveolus until final rupture takes place?

I offer these suggestions in the hope that pathologists may throw some light on a subject which is rather obscure at present, in spite of the fact that fortunately very few cases of idiopathic spontaneous pneumothorax ever reach the autopsy table.

Should agreement in regard to pathogenesis of this condition ultimately be reached on one or more of the elements enumerated, one still would be faced with the challenge concealed in the problem—why does idiopathic spontaneous pneumothorax show an overwhelming predilection for the male sex, chiefly in the age group twenty to thirty years, and why does it select the tall and slender?

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## SUBTOTAL PANCREATECTOMY FOR HYPOGLYCEMIA<sup>1</sup>

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The concept of hyperinsulinism began in 1924 with Harris' description of the clinical findings and its possible hormonal connotations (1). Although Warren (2) two years later collected 20 cases of adenoma of the islands of Langerhans, its relationship to hyperinsulinism was not realized until the following year when Wilder, Allen, Power and Robertson (3) presented anatomic evidence to support Harris' conception. They reported the first case of hypoglycemia due to a tumor (carcinoma) of the islands of Langerhans with operative and autopsy findings to substantiate its insulin producing character. In 1928, Thalheimer and Murphy (4) reported a case with low blood sugar levels and symptoms of hypoglycemia in which a carcinoma of the islet cells was found at post-mortem examination.

A benign tumor of the islands of Langerhans as a cause of hypoglycemia was proven at necropsy by McClenahan and Norris (5) in 1929. Six months later the first cure by operation of a case of hyperinsulinism, diagnosed clinically as due to a tumor of the islet cells, was reported in detail by Howland, Campbell, Maltby and Robinson (6). Since then additional cases have been recorded in the literature, with excellent reviews on hypoglycemia, (7, 8, 9) hyperinsulinism and islet cell tumors (10, 11, 12).

David (13), in 1940, collected 57 cases of hypoglycemia for which resection of the pancreas was done after careful search failed to reveal any evidence of tumor. He gathered 14 cases in which a tumor was found after partial resection and 3 cases in which it was found after subtotal resection. In 4 cases of subtotal resection no tumor was found at the primary operation but, in each instance, one was demonstrated at a later date. In 19 cases of partial resection, no tumor was found and the pancreas was either normal or presented hyperplasia of the islet cells. The pancreas was normal or showed hyperplasia of the islet tissue in 17 cases of subtotal resection. The case here reported is one in which all the criteria for diagnosis of islet cell tumor were satisfied. When no tumor was found after careful exploration of the pancreas, a subtotal pancreatectomy was done. Microscopically normal pancreatic tissue was found.

### CASE REPORT

*History* (Adm. 496588). L. M. a 36 year old dairy clerk was admitted to The Mount Sinai Hospital on October 15, 1942. Sixteen months prior to admission, while walking in the street, he suddenly developed weakness, diplopia, and syncope. Two months later a similar episode occurred following which more frequent and severe attacks of weakness were experienced, associated with hunger. He found that, occasionally, these symptoms could be averted by eating some food, especially chocolate. Six months after the onset, while in a restaurant he lost consciousness and was taken to a hospital. Soon after re-

<sup>1</sup> From the Surgical Service of Dr. John H. Garlock, The Mount Sinai Hospital, New York.

covery, attacks began to occur regularly before breakfast, often before getting out of bed. He would lose consciousness for as long as twenty hours and convulsive movements were occasionally noted by his mother. Two months later, after investigation at another hospital, a diagnosis of hypoglycemia was made and he was placed on a ketogenic diet to which he responded for a period of one month. He was referred to a mental health clinic, but nothing was found to account for his symptoms. The morning of admission, after having had his usual breakfast, he went to the Out-patient Department where he suddenly lost consciousness and was brought to the Reception Ward in an unresponsive state.

*Examination.* The patient was a well developed, obese, male; pallid, sweating profusely, and with marked generalized tremors. A healed thoracotomy scar was seen on the left chest and a few atelectatic râles were heard at the left base. His blood pressure was 120 systolic and 85 diastolic. The liver was palpable beneath the right costal margin and there was atrophy of the left testicle.

*Laboratory data.* Blood: hemoglobin, 110 per cent; 6,000,000 erythrocytes; 7,300 leucocytes, with a normal differential cell count. Wassermann test, negative; urea nitrogen, 12 mg. per cent; sugar 20 mg. per cent; cholesterol, 220 mg. per cent. Erythrocyte sedimentation rate, normal. The urine showed a faint trace of albumin and 5 per cent sugar. A cephalin flocculation test was negative. An electrocardiogram and x-ray examinations of the sella turcica and genito-urinary tract were normal. Electroencephalography revealed a hypoglycemic cerebral reaction, with spontaneous appearance of bursts of delta activity and a pronounced stuporous state brought on by hyperventilation, and with a return of the normal electroencephalogram and mental clearing following the intravenous injection of 50 per cent glucose. A Janney glucose tolerance test revealed a diabetic type of response, the blood sugar level rising sharply from 30 mg. per cent at fasting to 110 mg. per cent in a half hour and reaching 160 mg. per cent at the end of three hours. A galactose tolerance test was normal.

*Course.* The patient was placed on a high protein diet with frequent feedings and sweetened fluids. Daily blood sugars ranged from 25 mg. per cent to 35 mg. per cent and further investigations were vitiated by the fact that almost every morning before breakfast he went into incipient shock-like states. Within minutes after intravenous injection of 50 per cent glucose he returned to normal. After two weeks, during the latter part of which time attacks were prevented by frequent feedings he was transferred to the Surgical Service where it was felt that exploration was indicated because of the unremitting character of his symptoms.

*Operation* (Dr. John H. Garlock). The abdomen was opened through a long upper transverse incision and the lesser sac exposed by incising the gastrocolic ligament. The stomach and colon were then retracted bringing into view the entire body and tail of the pancreas. Careful palpation of this portion of pancreas failed to reveal anything suggesting a tumor. The peritoneum was incised along the inferior border of the pancreas and the organ was dissected upwards in order to expose its posterior surface. The pancreas was finally suspended from the splenic vein and artery and still no tumor was found. Once more the peritoneum was incised; this time along the outer border of the second portion of the duodenum. The duodenum, head, and neck of the pancreas were displaced mesially thus affording the operator an excellent opportunity to palpate this section of the organ. Again there was nothing to suggest the presence of an adenoma. The uncinate process was next exposed and found to be normal. After considerable discussion with the attending medical staff it was decided to perform a subtotal pancreatectomy. This was done by freeing the pancreas from the splenic vein and artery up to the neck at the point where the superior mesenteric vessels cross over the tip of the uncinate process. The pancreas was ablated at the neck and the edges closed over with silk sutures.

*Pathological report.* There were no significant changes in the microscopic appearance of the gland.

*Postoperative course.* The patient's temperature rose to 102°F. and returned to normal at the end of the first week. On the thirteenth postoperative day a considerable amount

of purulent material was evacuated from the wound and, following tube drainage and irrigation, the discharge ultimately became minimal. A glucose tolerance test done two weeks after operation showed a fasting level of 15 mg. per cent rising to level of 125 mg. per cent in one hour and falling to 50 mg. per cent in four hours. To avert possible hypoglycemic attacks the patient was given large amounts of glucose. Subsequent blood sugar levels averaged 70-85 mg. per cent and he remained completely free of symptoms. On November 23, 1942 he was discharged for convalescent care.

*Second admission* (December 30, 1942). *Interval History:* During the greater part of the next five and one-half weeks at the convalescent home he suffered from dizziness almost every day. One week before his readmission, he suddenly became unresponsive but was completely relieved by the ingestion of food. Four days before admission he lapsed into unconsciousness upon arising from bed and from then on became dizzy before each meal. Examination disclosed evidence of the 30 pound loss in weight since the operation. A small granululating sinus at the right angle of the wound covered with mucopurulent material was seen. Fasting blood sugar levels averaged 50 mg. per cent on a high protein, high fat diet. Oral and intravenous Janney tests were productive of the diabetic type of response. A galactose tolerance test was normal and an adrenalin tolerance test included a rise in the blood sugar from 110 to 130 mg. per cent after injection of adrenalin. His basal metabolic rate was minus 6 per cent. Electroencephalography gave a normal fasting record before and after hyperventilation. While on the ward the patient received a high protein, high carbohydrate diet, and evening feedings before retiring. He was awakened during the night for additional small feedings. On this regimen no acute hypoglycemic episodes occurred. Occasionally during long, fasting periods transient weakness, slight vertigo, diplopia and unresponsiveness were noted. The wound was controlled by tube drainage and he was discharged on February 3, 1943.

*Third admission* (February 19, 1943). The patient reentered the hospital with a recurrence of severe symptoms, including beginning loss of consciousness and on one occasion twitching of his left hand. He was unable to arise in the morning unless he was given orange juice. Examination showed that the wound had not changed in appearance and that a pancreatic fistula was present. During the first few days in the hospital he had repeated episodes of disorientation, unresponsiveness, and weakness, occasionally with convulsive movements; despite a high protein diet with in-between and night feedings. He was given adrenalin intramuscularly at first once, then twice a day and subsequently ephedrine was added. On this therapy he was asymptomatic. In order to determine how much of this medication was necessary all drugs were withdrawn and the patient was maintained on a high protein diet with additional feedings. He was without symptomatology on this regimen for two and one-half weeks and was discharged on March 19, 1943 with dietetic instructions.

*Follow-up.* On March 17, 1943 the patient was admitted to the ward for two days while the fistulous tract was probed and drained. He was seen again on June 1, 1943 in the follow-up clinic where it was observed that he had gained 15 pounds. He stated that during the previous two weeks he had had several hypoglycemic attacks.

Dr. Garlock plans to explore the patient again in the hope of demonstrating an adenoma of the remaining portion of the pancreas.

#### DISCUSSION

The syndrome presented is clearly that of hypoglycemia. Investigations demonstrated no obvious endocrine disturbance causing such change in sugar metabolism. X-ray examinations of the sella turcica and genito-urinary tract revealed no gross pathology in the pituitary or adrenal glands and the clinical picture did not conform to disturbances of these organs. With a normal basal metabolic rate, hypothyroidism was ruled out. No imbalance of the vagus or

sympathetic nervous systems could be demonstrated to account for the symptoms. The tests of liver function and the adrenalin tolerance test appeared to exclude hepatic disease and inability to mobilize liver glycogen. At the same time normal elevations of blood sugar and maintenance of levels following oral or intravenous administration of glucose seemed to rule out faulty absorption as the etiologic factor. Furthermore, it has been shown (12) that, in 70.5 per cent of cases of proved adenoma of the pancreas, the glucose tolerance test produces a diabetic type of response. It was not believed that this was a case of functional hyperinsulism for, in this latter condition, the attacks are not associated with low levels of fasting blood sugar. Also the depression of the fasting blood sugar level by provocative tests is no greater here than that produced in normal individuals (9).

On the other hand, the case did satisfy Whipple's criteria for the diagnosis of islet cell tumor of the pancreas (14): 1) Post-absorptive blood sugar levels below 50 mg. per cent; 2) hypoglycemic attacks when the patient is fasting (intolerance for fasting); 3) relief of the attack by administration of glucose; to these may be added 4) normal health and stability of the autonomic nervous system before the first hypoglycemic attack (Wilder (15)); and finally the obvious corollary: absence of extrapancreatic causes of hypoglycemia. In the light of these facts, and because of the deleterious effects which might be produced on the nervous system by long standing or repeated attacks of hypoglycemia, as well as the creation of increasing technical difficulties by the increasing obesity, exploration of the pancreas was deemed advisable.

In an analysis of the cases in the literature (13, 16) where no demonstrable tumor could be found, as in our case, it was revealed that the surgeon had to assume, first, that the pancreas was normal and that perhaps the hypoglycemia was of extrapancreatic origin, second, there might be diffuse hyperplasia or hyperfunction of the islands of Langerhans, and third, a small adenoma buried deep within the gland might escape detection because of its location or because the consistency of an adenoma differs very little from that of the pancreas (17). The surgeon then performed a partial or a subtotal pancreatectomy with the hope that a tumor might be found in the resected portion; that hyperplasia of the islet cells might be present; that removal of a large part of the insulinogenic tissue of the pancreas, particularly the body and tail would diminish the insulin secreting power of the gland so that the hypoglycemic symptoms, whatever their etiology, might be completely relieved or at least brought under partial control.

There are many case reports of relief of symptoms after partial or subtotal pancreatectomy where normal pancreatic tissue was removed (13). Each report of such a case has prompted mechanistic hypotheses to explain the result and has drawn analogies to support them. Graham (quoted by Womack (8)) pointed out the possibility of a pancreas with normal appearing islets anatomically showing, on assay, an insulin content much greater than normal. Until further evidence is at hand, the results of resection of the pancreas cannot be considered in terms of proportion of islet tissue removed. The analogy of such

resection in hypoglycemia to the administration of insulin in diabetes suggests that it is a question of dosage (8). Just as in the treatment of this condition an insufficient amount of insulin is valueless, so in hypoglycemia removal of an insufficient amount of pancreas would be of little value. It is thought (18) in these cases, then, that the hypoglycemia is the result of functional overactivity on the part of the islet cells just as in diabetes without sufficient histologic islet changes, it is thought that underproduction of insulin exists, and, therefore, it is logical to resect as much of the islands of Langerhans as possible. It becomes a simple matter to draw a further analogy between hyperinsulinism with hypoglycemia and hyperthyroidism with its effects. The accomplishments of adequate therapeutic results in the surgical treatment of hyperfunction of the thyroid is most often associated with subtotal thyroidectomy. Thus, removal of part of the pancreas should have just as much effect in the relief of hypoglycemia as does removal of part of the thyroid in Graves' disease and failure of relief is due to too little resection of pancreatic tissue (19). This comparison seems hardly tenable in those cases with unsatisfactory results where even at autopsy no adenoma of the pancreas is found, as in the case described by Seckel (20).

Where a case of hypoglycemia is not benefited by subtotal pancreatectomy one may assume an extrapancreatic cause. However, when Whipple's "essential triad" is present, and subtotal pancreatectomy fails, one must assume the presence of an adenoma in the unresected portion regardless of how little remains, as recently stated (22) in aberrant pancreatic tissue. This is proposed by the evidence at reoperation and/or necropsy (14). And if an adenoma is removed and the symptoms remain unchanged, reoperation may disclose a second tumor (Graham, quoted by Wilder (15)).

It is evident from the literature that the end-results of operation in cases with islet cell tumors are excellent, and in patients without adenomata the results while not as satisfactory are sometimes gratifying. The result in our own particular case was disappointing. In the cases collected by David, mentioned above, where no demonstrable tumor was found grossly and microscopically and the pancreas was resected, the incidence of relief was 2 out of 15 cases for partial pancreatectomy and 10 out of 14 cases for subtotal resection. These cases raise the question as to whether the "diagnostic triad" is pathognomonic of islet cell adenoma. Such hyperinsulinism without known pathologic basis exists, states Brunschwig (21).

#### CONCLUSIONS

Every case of hypoglycemia presenting Whipple's triad of symptoms, where extrapancreatic causes have been excluded, where medical management has failed, and, where subtotal pancreatectomy has been performed in the absence of a tumor, should be reported irrespective of result because of the information it yields towards the clarification of the problem of hyperinsulinism. It would seem, from the literature, and our case (although unproven), that in the presence of an adenoma regardless of its dimensions or even where some extrapancreatic

cause is responsible, no matter how much pancreatic tissue is removed, symptoms will persist. Until a definitive method for differentiating organic from functional abnormalities of the islands of Langerhans, especially those due to imbalance between interrelated endocrine organs, is found, disappointing results similar to ours will be obtained.

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## HYPOGLYCEMIA AND HYPERINSULINISM; WITH SOME REMARKS ON ELECTROENCEPHALOGRAPHY<sup>1</sup>

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Ever since Seale Harris called attention to the syndrome of hypoglycemia, the clinical diagnosis of hyperinsulinism has become almost commonplace and that of adenoma of the pancreas fairly simple. In many instances a correct diagnosis may be ventured after an office examination without the aid of the laboratory, provided one bears the condition in mind and takes a detailed history. Indeed of the five cases of adenoma of the pancreas which one of us (W) has seen the diagnosis was made after one examination in four, afterward verified by laboratory studies and by operation. The first case, which was characterized essentially by convulsions and diagnosed only at necropsy, was missed because of lack of familiarity at that time with the syndrome and the special nature of the hypoglycemic seizures. Three of the patients had been treated as psychoneurotics and two as epileptics.

Quite a number of patients with hyperinsulinism and occasionally some with adenoma of the pancreas are first seen by the neurologist. They are generally referred with the diagnosis of hysteria, sometimes because of character and personality changes or some vague psychosis, rarely with non-descript chorea or other mild dyskinesia, and occasionally with the convulsive state. The erroneous diagnoses are generally arrived at because the examiner finds no clinical evidence of organic disease and fails to evaluate the psychiatric picture or the nature of disturbances in consciousness and the convulsive seizures.

We do not wish to enter here into a discussion of the differential diagnosis of psychoneurosis and hypoglycemia<sup>2</sup>, but we should like to say a word about the nature of the hypoglycemic convulsion and the state of unconsciousness. Whereas the average epileptic seizure is ushered in quite suddenly with or without an aura, is characterized by more or less typical convulsions and especially complete unconsciousness, is terminated fairly rapidly, and is followed by total amnesia, the hypoglycemic fit may lack all these features. Its onset generally is slow, the patient slumping into it as it were. The patient gradually becomes drowsy, may speak in mumbling fashion or carry out purposeless acts, and eventually goes to sleep or becomes totally unconscious. Convulsions may be absent, and, if present, are not of the typical tonic-clonic variety but consist of a bizarre thrashing about. There generally is no tongue-biting, the coma does not end rapidly or suddenly but is terminated either by the administration of sugar or the patient spontaneously emerges from it in a weak and confused state. It is in the pre-convulsive state that the picture simulates hysteria, an agitated depression or a confused psychotic state. It is here that detailed investigation

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<sup>2</sup> This, as well as more detailed electroencephalographic correlations, will be taken up in a separate publication by Wechsler and Strauss.

into the history comes to one's aid. On careful analysis it is found that the patient has been hungry for some time before the episode or that he has a craving for sugar or other sweets. For this reason the hypoglycemic episode is apt to occur in the morning after the night fast or later in the afternoon after a small midday meal.

If the convulsive seizure or the coma is not typical the disturbance in brain rhythm is. This holds true as much for the hypoglycemic state without shock as during the periods of shock, although it is clearly more striking in the latter than in the former. This refers to the electroencephalographic tracings, to which we should like to call attention as one very important additional diagnostic criterion both for hypoglycemia and hyperinsulinism. It will be recalled that the Whipple "triad" for the diagnosis of hyperinsulinism consists of: 1) attacks of insulin shock; 2) a fasting blood sugar of less than 50 mg.; and 3) relief of symptoms after the intravenous administration or oral ingestion of sugar. The fourth diagnostic point, therefore, is the presence of an electroencephalographic tracing of an epileptic nature. The important feature of this is its prompt return to normal after the administration of sugar. More important is the fact that while the electroencephalographic record is consistently abnormal during the hypoglycemic state of hyperinsulinism, even though it is temporarily normalized by the ingestion of sugar, the record becomes permanently normal after the successful removal of a pancreatic adenoma. The electroencephalogram, therefore, is not only an absolute diagnostic criterion but a test of the success of the operation. A glance at the tracings in the two cases presently to be described will clearly demonstrate this fact.

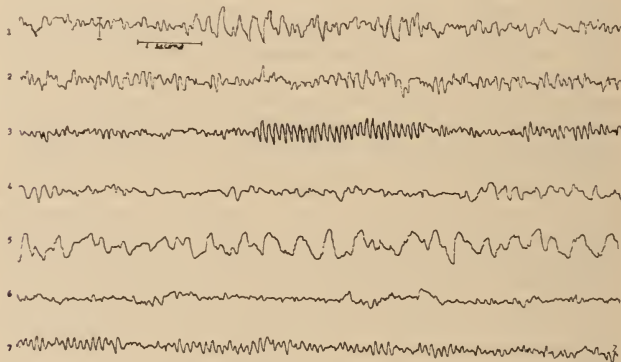
If, after partial pancreatectomy, the electroencephalographic record is still abnormal it signifies that either the adenoma was not removed or that another one is still present or that the hypoglycemia was not the result of hyperinsulinism caused by an adenoma. It is obviously important, then, to look in all cases for other causes of hypoglycemia before operation is undertaken. Without going into the details of differential diagnosis, we should merely like to mention, what is already well-known, that disease of the liver, more particularly hepatitis, may cause hypoglycemia; that some "psychoneuroses" may be the expression of hypoglycemia not due to adenoma of the pancreas; that disease of the brain, namely of the hypothalamic vegetative centers, may give rise to disturbances in sugar metabolism and hypoglycemia; and that affection of the glands of internal secretion, the pituitary-thyroid-adrenals, can produce hypoglycemic states.

We should also like to add a fifth diagnostic criterion in the study of hypoglycemia due to hyperinsulinism, namely, the glucose tolerance test which gives rise to what is known as the paradoxical or diabetic curve. While in most cases of hypoglycemia the blood sugar rises rapidly from the fasting state and falls rapidly in a sharp curve to the original level, in those due to hyperinsulinism there is the rapid rise but not the rapid fall. The curve remains consistently high for a longer period of time in the same manner as in the hyperglycemia of diabetes, and drops slowly and to a higher level than that of the fasting state. The explanation for this is not clear.

The following two cases will illustrate some of the points thus far discussed.

## CASE REPORTS

*Case 1. History* (Adm. 498617): D. K., a white, unmarried woman of 28 was seen in the office for the first time on December 1, 1942 with the complaint that she had no energy and felt tired all the time. She stated that she was perfectly well until September 15, 1942 when she woke up feeling weak, empty, dizzy, nauseated, and sleepy. She stared and mumped. She was given food and recuperated in about two hours. Though she was not unconscious she did not remember the details of the incident. A similar episode occurred about a month later after she had fasted the day before. She was again free of symptoms



Electroencephalograms in 2 cases of spontaneous hypoglycemia. All the records are taken with fronto-occipital leads. Calibration equals 100 microvolts.

Records 1-3, Case 1.

Records 4-7, Case 2.

RECORD 1. Fasting: the record shows numerous potentials with frequencies of 6 per second and runs of high voltage activity with a frequency of close to 4 per second.

RECORD 2. After injection of 30 cc. 50 per cent glucose solution intravenously: the high voltage, low potentials have disappeared.

RECORD 3. Fasting: 19 days after operation. Normal record.

RECORD 4. Fasting: runs of 6 per second activity.

RECORD 5. Fasting: after hyperventilation. Continuous high voltage, slow activity with frequencies between 2 and 3 per second.

RECORD 6. After injection of 50 cc. 50 per cent glucose solution intravenously: the slow potentials have disappeared.

RECORD 7. Hyperventilation after the injection of 50 cc. 50 per cent glucose solution intravenously. No slow activity appears.

for a month when she had several similar attacks, all in the morning, occurring November 21, 26, 28 and 30. She was told that she was irrational during the spells, slept for two or three hours, and recovered after partaking of food. She had no other complaints and had never been ill before. She was sent to the hospital with the diagnosis of convulsive state due to hypoglycemia, probably on the basis of adenoma of the pancreas.

*Examination.* The general physical and neurological examination showed nothing abnormal. She was well developed, somewhat obese, and presented general hirsutism. Cerebrospinal fluid, blood and urine examinations and skull roentgenograms were normal. The basal metabolic rate was minus 1 per cent. The fasting blood sugar on the

first examination was 20 mg., and ranged from 30 to 50 mg. during the preoperative stay in the hospital.

*Course.* After a special test fast she became querulous, tearful, mumbled incoherently, and complained of hunger and drowsiness. Electroencephalogram at this time showed a large amount of 4.5 to 6 per second delta activity. After the administration of 15 grams of glucose intravenously, she promptly returned to normal, and the abnormal delta activity disappeared. On December 9, after fasting for 16 hours she was given twenty units of insulin, whereupon she became drowsy, disoriented and uncooperative. A glass of orange juice restored her to normal. Salt tolerance studies and liver function tests excluded adrenal and hepatic involvement.

*Operation:* (January 6, 1943). A reddish tumor measuring 1.5 cm. in diameter was found in the tail of the pancreas. The tail of the organ including the tumor was resected. No other tumors were demonstrable. On microscopic study the tumor was proved to be an adenoma of islet tissue.

The patient made an uneventful recovery except for a slight wound infection at the left end of the transverse incision. The fasting electroencephalogram promptly returned to normal as did also the blood sugar tolerance tests. The Janney test which before operation showed the paradoxical curve returned to normal.

#### *Before Operation—Blood Sugar*

December 2.....	20 mg. %
December 3.....	45 mg. %
December 9.....	40 mg. %
December 14.....	50 mg. %
December 16.....	40 mg. %
January 3.....	30 mg. %

#### *December 2—Janney Test*

Fasting blood sugar.....	20 mg. %
9 A.M. given 110 grams glucose	
½ hour later, blood sugar.....	150 mg. %
1 hour later.....	190 mg. %
2 hours later.....	250 mg. %
3 hours later.....	210 mg. %
4 hours later.....	150 mg. %
5 hours later.....	90 mg. %

#### *December 9—Insulin Tolerance Test—10 A.M.*

Fasting blood sugar.....	40 mg. %
10:05 A.M. 10 units of insulin	
10:20 A.M.....	40 mg. %
10:55 A.M.....	40 mg. %
11:45 A.M.....	20 mg. %

Patient dazed, speech thick; given glucose, recovered.

#### *After Operation—Blood Sugar*

January 8.....	105 mg. %
January 12.....	80 mg. %
January 15.....	70 mg. %
January 23.....	90 mg. %
January 27.....	80 mg. %
February 1.....	70 mg. %

*February 27—Sugar Tolerance Test*

Fasting.....	80 mg. %
$\frac{1}{4}$ hour.....	85 mg. %
1 hour.....	180 mg. %
2 hours.....	150 mg. %
3 hours.....	155 mg. %
4 hours.....	170 mg. %
5 hours.....	120 mg. %

*Case 2. History* (Adm. 496588). L. M., a white man, aged 36, was admitted to the hospital on October 15, 1942. He had been well up to about June 1941 when one day he suddenly felt weak, saw double, and "things went black before his eyes." He quickly recovered and was well for two months. In August of the same year he had a similar fleeting episode. Since then the attacks occurred with increasing frequency. He made the observation that they happened most often when he was hungry and that he could avert them by eating, especially chocolate. Once he lost consciousness, he was taken to a hospital and, because "nothing was found," was referred to a psychiatric clinic. The attacks began to occur before breakfast. On one occasion he was unconscious for twenty hours, on several other occasions he had twitchings, fell out of bed and bruised himself; but he never bit his tongue or had incontinence. A diagnosis of hypoglycemia was made at another hospital and he was placed on a ketogenic diet, following which he was well for one month. The attacks then recurred. The morning of October 15, 1942 while in an out-patient clinic, he suddenly lost consciousness, and was sent into the hospital.

*Examination.* The patient was unresponsive and pale, he perspired freely and had generalized tremors. Except for obesity, the finding of the liver edge two fingers breadth below the costal margin, and an atrophic left testicle, neither the general physical nor the neurological examination showed anything abnormal.

*Laboratory data.* The blood sugar was found to be 20 mg. per cent. He was given adrenalin, intravenous glucose and orange juice by mouth and he recovered consciousness. The Janney curve on October 16, 1942 was as follows:

Fasting, 9:30 A.M. ....	10 mg. %
Sugar ingested 9:30 A.M.	
10 A.M.....	90 mg. %
10:30 A.M.....	100 mg. %
11:00 A.M.....	90 mg. %
11:30 A.M.....	70 mg. %
12:30 A.M.....	35 mg. %

An electroencephalogram done in the fasting state on October 17, showed bursts of  $2\frac{1}{2}$  per second delta activity of 150 microvolt magnitude, lasting up to three seconds. After twenty seconds of hyperventilation, the delta activity became continuous, and after two minutes the patient stopped responding. He was given 50 cc. of 50 per cent glucose intravenously, whereupon he became clear mentally and the electroencephalogram showed complete disappearance of delta activity. Hyperventilation now failed to bring out an abnormal record.

*Course.* For two weeks following his admission, the patient showed symptoms of incipient shock on several occasions, always with a blood sugar below 40 mg. per cent and invariably relieved by the administration of glucose. Liver function studies and adrenalin tolerance tests apparently ruled out hepatic and adrenal involvement. On October 31 the patient was explored for adenoma of the pancreas. A careful search of the entire pancreas following extensive mobilization of the organ failed to reveal the presence of a tumor. It was therefore decided to carry out a subtotal pancreatectomy. The tail and the body of the organ were excised after ligation of the blood vessels. Microscopic examination of the excised pancreas showed no evidence of adenoma. On November 5 the fasting blood sugar was 30 mg. per cent and the Janney test five days later showed the same figures obtained one month previously. He was discharged on November 23.

He was again admitted to the hospital on December 30, 1942 because of recurring episodes of vertigo and unresponsiveness relieved by fruit juice, and loss of twenty pounds in weight. Re-examination and further complete study showed practically the same findings as on the previous admission. The patient was given a high protein and high carbohydrate diet, he was fed before retiring and awakened during the night for additional feeding. As long as this routine was maintained no hypoglycemic shocks occurred, but when the patient was made to fast for the purpose of tests, they recurred immediately. The patient was discharged with the diagnosis of hypoglycemia of unknown etiology. He was readmitted on February 19th, 1943 because of further recurrence of symptoms. This time he showed repeated episodes of disorientation, unresponsiveness and weakness, and occasionally convulsive movements despite the high protein-carbohydrate diet and numerous feedings. When these were supplemented by injections of adrenalin in oil twice a day and ephedrine three times daily, he remained free of attacks for two and one-half weeks. He was then discharged, only to be admitted once again on July 23, 1943 because of recurring attacks. In spite of all measures he continued to have the attacks described above. On one occasion the hypoglycemic reaction continued after the intravenous administration of glucose. In view of this it was felt that a pancreatic adenoma must be present and operation was advised. The patient refused, and he was discharged on September 12, 1943.

#### SUMMARY

Both cases presented the syndrome of hypoglycemia, but, while they showed a number of similarities, there were also certain differences. Hypoglycemic shocks occurred in both, the fasting blood sugar was equally low, the electroencephalographic tracings were characteristic in each, and for a time they responded alike to the administration of sugar. Studies in both cases apparently pointed to hypoglycemia of hyperinsulinism. And yet an adenoma was found in the first, none in the second; the paradoxical "diabetic" curve was present in one and not in the other; whereas removal of the adenoma brought about a complete cure in Case 1, subtotal pancreatectomy accomplished nothing in Case 2. Indeed the syndrome in the second case progressed to the extent that even the administration of sugar, high protein-carbohydrate diet and adrenalin failed to give relief. What is most important, the electroencephalographic record continued to be abnormal. It is possible, of course, that an adenoma is still present, though it should be stated that the pancreas was completely exposed at operation and a most careful search was made.

It is difficult to reconcile the differences in view of the identity of the clinical syndrome in both patients. Evidently the preoperative diagnosis of adenoma of the pancreas is still not absolutely certain despite the very definite criteria laid down. That is why we should like to add to Whipple's triad a fourth one, namely, a consistently abnormal electroencephalogram before operation with temporary return to normal following the administration of sugar, and a permanently normal one after operation. The presence of an abnormal electroencephalogram and its return to normal on the administration of sugar merely proves that there is hypoglycemia. It is confirmatory and diagnostic of pancreatic adenoma. A fifth point may be the presence of a paradoxical Janney curve in hypoglycemia due to hyperinsulinism of adenoma and its absence in hypoglycemia of other origin.

THE GERONTOCOMIA OF GABRIELE ZERBI  
A FIFTEENTH CENTURY MANUAL OF HYGIENE FOR THE AGED  
FREDERIC D. ZEMAN, M.D.

[New York City]

*Miss not the discourse of the aged, for they also learned of their fathers:  
because from them thou shalt learn understanding, and to give answer in  
time of need.*

*Ecclesiasticus.*

Some years ago, while compiling a bibliography on the medical aspects of old age, the writer encountered the following entry in the Index Catalogue:

ZERBI (Gabriele) ( —1505) *Ad Innocentiam viii Pon. Max. gerontocomia feliciter incipit. Prologus. (Ad finem:) Impressum Rome per Eucharium Silber alias Franck; Anno Domini MCCCCLXXXIX. 134; 1. sm.4° (1).*

Reference to Garrison yielded the information that "Gabriele Zerbi (1468–1505) of Verona, professor at Padua, who wrote an anatomic treatise (1502), first separated the organs into systems, was the first to treat of infantile anatomy, and described the muscles of the stomach and the puncta lachrymalia" (2). In another place Garrison characterizes Zerbi's *Cautelae medicorum*, published in Venice in 1495, as one of the best medieval treatises on medical etiquette. It was therefore clear that the author of *Gerontocomia* was a man of outstanding ability and reputation in his own day. Interest in finding out more about him was stimulated by Garrison's omission of any mention of the work on old age. This was then found to be true of Castiglione (3), Pagel (4), and Neuburger (5), as well as the numerous eighteenth and nineteenth century authors who treated of longevity and the senium, such as MacKenzie (6), Hufeland (7), Sinclair (8), Canstatt (9), Geist (10), and Durand Fardel (11). De Renzi (12) mentions the book in his account of Zerbi, but dismisses it simply as a work on old age. Bibliographical references are not uncommon, being found in Haller's *Bibliothecae medicinae practicae* (Berne, 1776), in Plouquet's *Initia bibliothecae medico-practicae* (Tubingen, 1793–97) where it is referred back to Haller, and in various lists of incunabula such as Klebs' famous "Short list."

No evidence has as yet been discovered to indicate that this work has been read or quoted by any medical or lay writer since its publication. In fact, the only reference to Zerbi in recent periodical literature is Crummer's (13) paper on the *Anatomia Infantis* of Zerbi, which is largely devoted to a careful translation of this fragment from the larger anatomical work on which Zerbi's fame seems to rest. Crummer offers little information on Zerbi's life and does not mention his other writings.

The occurrence of a "lost" work on old age by an eminent Renaissance physician aroused further curiosity and kindled the desire to handle the book and to

sample its contents. These ambitions were gratified by visiting the Army Medical Library some time prior to the removal of the incunabula to Cleveland. The photograph (fig. 1) of the first page will reveal to the practiced eye the striking characteristics of an early printed book. The helpful erudition of a friendly scholar made possible the preparation of an abstract which forms the bulk of this communication and which will reveal Zerbi's clear understanding of the problems of old age, and his remarkably realistic approach to their alleviation.

GABRIELIS ZERBI VERONENSIS  
AD INNOCENTIVM. VIII. PON. MAX.  
GERONTOCOMIA FELICITER INCI-  
PIT. PROLOGVS.

Alitquo ac paterno oim fere pſſu natura ⁊ rōe  
ducente pſelluz eſt imenſo numine aliquo cūcta  
diſponi cui⁹ nutu ſūmoto tucri ſciſm pōt niſil. ſ  
numen deus ſiue quolibeat nomīne appelleſ perfectionis  
eius exuberantia oīa ſingulis vt decet impartit ⁊ abundā  
tius tribuit etſi ſepenumero ineptitudine eius qđ ſubſcīſ  
nequeāt adipiſci. Licz autē eſſe ipſum ⁊ viuere diuturnita  
tiſq; vite ⁊ ſalutis appetentia ſicuti ⁊ pfectōes alie a dco  
emanātes rebus nature pſtantibus cōdicent nulla bonita  
te que illis cōgruit retenta apud eū in primo rez exordio  
Hōmīni tñ vni animantiū oīm meliori (neſcio an dicam)  
eius ſato ſeu triftiozi adeo imenſam parens natura dedit  
viuendi cupidinem ⁊ ſocunditatē eius vite comites indi  
uiduas vt vitā hāc q̄ſuis temporalis ſit ac labore plenīſſi  
ma tā ſenes q̄ iuuenes cuplāt ⁊ hī qui miſeri ſunt nolunt  
interire etiā cū ſe miſeros eſſe ſentlāt. quo ſit vt hōim ple  
riq; ſenēſcere cupiant q̄ſuis ſenectutem accuſent adepti.  
Adco etiā blanda eſt ſpirandi p ſe cuiq; dulcedo vt nemo  
ſit tā ſenex morte etiā in ſoribus deplozate iam vite exſite  
cuilicz interpoſito metu ſpes tñ adhuc annue vite non ſu  
perſit. Nō expleſ autē cuiuſlibet hominis vita quam tan  
topere exoptant periodo equali paucis aut nullis eoz ad  
vlīmū humane vite finem naturalem imo viz ad ſenectu  
tis principia puenientibus deſidia nō modo ⁊ luxuria bo  
nos mores (vt aiunt) viſtiantibus quibus humana corpa  
aſiligi pſueuerūt verumetiam accidentibus pluribus atq;  
offenſaculis ſibi oppoſitis intercipiētibus prius vitā quo

FIG. 1. The first page of Zerbi's *Gerontocomia*, Rome, 1489. As in the earliest printed books, no separate title page is present. Title pages complete with name and address of printer and publisher and with the date, did not become common until 1520. (Photograph by courtesy of the Army Medical Library, Cleveland Branch.)

The facts about Zerbi's life are not easily ascertained, but a remarkably full account, based on contemporary Italian sources, now inaccessible, is to be found in the *Biographie Universelle* (14), (Paris, 1828). This biography even preserves the malicious gossip of Zerbi's professional competitors. From it we learn that he was born at Verona about the middle of the fifteenth century, the exact birth year being unknown. After having taught philosophy for some time at Padua and at Bologna, he went to Rome, preceded by a great reputation. One day,

according to the more probable story, he had the insolence, before a group of philosophers and theologians, to refer to Pope Sixtus IV as ignorant, and fearing the wrath of the pontiff, fled to Padua. His anatomical colleague, Berengario da Carpi ascribed his flight to his conviction of the theft of two silver vases from a bishop whom he was treating for an illness. This story has gained much currency, in spite of its unlikelihood. Whatever his motives may have been for leaving, it is known that he returned to Rome after an interval and that when he published his *Gerontocomia*, in 1489, the dedication was accepted by Pope Innocent VIII. In Rome he filled the chair of medical theory, apparently with satisfaction, since it is known that in 1490 his stipend was increased from 150 to 200 florins. After several years, he was invited to return to Padua to assume the chief professorship in medicine. He allowed himself to be tempted by an offer of 600 ducats, and in 1495 moved back to Padua, where his reputation is said to have attracted many students.

In 1505, a Turkish pasha, seriously sick, asked André Gritti, then doge of Venice, to send him one of the most capable physicians in Italy. Zerbi was induced to accept the commission which promised to be lucrative. At the end of a stay of several days, seeing his patient out of danger, Zerbi prescribed a regimen for his convalescence, and took his way back to Padua, loaded with magnificent gifts. But, hardly had he departed, when the pasha died. His slaves then pursued Zerbi to get back the riches he was carrying away, and having caught up with him in Dalmatia, killed him and his young son in the most barbarous fashion. On hearing this tragic news, Della Torre, a fellow-anatomist, is said to have remarked, that, having made all anatomists suffer by the obscurities of his style, Zerbi had now been made to endure suffering in his turn.

In addition to the *Gerontocomia*, Zerbi wrote *Quaestiones metaphysicae*, Bologna, 1482; *Cautelae medicorum*, Venice, 1495; and *Liber anatomiae corporis humanis et singulorum membrorum illius*, Venice, 1502. Dryander, in 1537, published the part of this work relating to the anatomy of the infant (see Crummer). For a detailed analysis of Zerbi's contributions to anatomy the reader is referred to Portal's *History of Anatomy* (15). Garrison in the quotation given in the opening paragraph has summed up Zerbi's claims to fame as an anatomist.

The work on old age will in our opinion show up an unknown side of Zerbi's ability, and in addition form an important link in the development of our medical knowledge of old age. It serves to give us a picture of medical attitudes, intermediate between the great Arab physicians and the clinicians of the early seventeenth century such as André du Laurens (16).

In his prologue, Zerbi politely wishes a long life to the Pope and explains that a guide book for old age is needed, since life is valuable and people desire to attain old age even though they are suffering from disease. *Gerontocomia* concerns itself with the proper regimen for old age, which has a special complexion, first of a cold and dry nature, later of a cold and humid nature. This is of course the doctrine of Galen which ruled medical thought about old age until approximately a century ago. Zerbi then points out that this complexion predisposes to more than 300 different diseases, and enumerates almost word for word the famous

list found in the Hippocratic aphorism: "Old men suffer from difficulty of breathing, catarrh accompanied by coughing, strangury, painful micturition, pains at the joints, kidney disease, dizziness, apoplexy, cachexia, pruritus of the whole body, sleeplessness, watery discharge from the bowels, the eyes and the nostrils, dulness of sight, cataract, hardness of hearing" (17). He questions Pliny's opinion that a sudden death is the best fate for man, and plans the discussion of the means of retarding old age in the 57 chapters that follow. He complains, as has nearly every other writer on the subject, from the earliest times to the present, that there has been no extensive discussion of old age problems in the previous literature, and that most medical writers have touched only casually on the hygiene of the old.

The first chapter defines old age by dividing it into two periods of which the first, latent old age (*senectus prima*) lasts from 30 to 60 years and is under the influence of the planet Jupiter; the second, manifest old age (*senectus decrepita*) is under the influence of Saturn. In chapters 2-6 are described the causes of early senescence, of wrinkles, baldness and gray hairs, the signs of approaching old age. Chapter 7 deals with the duration of life. The author believes that the length of life depends on the stars and on the individual constitution of the body. The year 63 is the critical year of old age, and it is called the "scalarium." Old age is inevitable (chapter 8), but its end is uncertain (chapter 9). Much depends on the innate and natural disposition of the individual; males live longer than females (chapter 10).

Zerbi emphasizes that, since life cannot be extended beyond its natural limits, gerontocomia should aim only at retardation. It is a special art consisting of conservative and preservative measures, and the use of the six "res naturales" (chapters 11-13). The master of this art, a specialist in old age, is termed "Gerontocomus." His qualifications and duties, as well as those of his assistants are described. He should be humane, of advanced age, familiar with medicine, frugal, moral, experienced, religious, clean, moderate in eating, of good habitus, well groomed, without body odors or excessive perspiration. By his own behavior he should set an example of the proper conduct of an elderly man. He should inspect the urine of people daily.

The staff-servants should be home-lovers, not gluttonous, abstinent, and chaste. They should care for the dressing and cleanliness of the old, should not be loquacious, should be quick and agile, should inspect the foods of the old, and should not stay up too late at night. Certain nationalities are more suited for such work than others. English, Swiss, Illyric and Hungarian servants will not do. The best are the Britons, some French, Spaniards, and Italians, especially the Lombards.

In chapter 15 the best location for homes for the old is discussed. Generally, the temperate climate is the best, also the eastern exposure. The mansion should be on healthy ground with ample access to the wind for good ventilation. The bedroom should be in the best ventilated part of the dwelling. The author recommends that the old should not be exposed to direct fire, because it may cause indigestion, visual troubles and vertigo.

In the following chapters (16-56) rules for exercise, bathing, rest, eating and drinking, sleeping, body evacuations and mental health are described. The last few chapters recommend the meat of the viper, broth, distillate of human blood, gold solutions, precious stones and syrups for the retardation of old age. Chapter 57 discusses the inevitable death.

Particularly noteworthy is the advice given in chapter 27 for using human milk as a nutritive measure for the old. A good strong woman between 25 and 35 years of age, who is about one or two months post-partum, should be used, and Zerbi advises that the old suck the milk directly from the mammae of the woman. That this is a practice grounded in remote antiquity seems probable but the writer is not familiar with any direct references. There come to mind, however, two modern books in which it is mentioned, one a biography and the other a novel. In O'Connor's *The Astors* (18), the author describes the 84 year old John Jacob Astor, as he lay moribund in 1845: "... despite the golden flow into his coffers, his palsied hands must seek the breast of a wetnurse for his nourishment." In Steinbeck's *The Grapes of Wrath* (19), the feeble old man is nourished by the girl who has lost her baby.

In chapter 42 Zerbi, discussing the mental health of the old, strikes a note that seems wholly modern until one recalls that as far back as 124 B.C. Asclepiades of Bithynia recommended music and occupational therapy for mental sufferers (20). Zerbi considers music an excellent measure for cheering up old people. Bedtime stories and other tales are also important, but cautions that the teller be expert, and a discriminating judge of stories. Conservation of sight is to be achieved by proper illumination and the use of certain colors. The sense of smell is to be stimulated by aromatics and the burning of incense. Sexual intercourse (chapter 43) is prohibited, except in latent old age—when extreme moderation is advised. Since there is little superfluous in an old body, strength should not be dissipated by coitus.

The foregoing condensation of Zerbi's text serves to give us the spirit of the author, and impresses us with his sanity and commonsense. His practical recommendations seem to be based on actual personal experiences, and thus his work is to be differentiated from the obvious paraphrases of Hippocrates, Galen and Cicero which became common later in the sixteenth century. His description of the qualifications of a physician specializing in the diseases of old age is particularly striking at this time when the profession is regarding old age with renewed interest.

An account of Zerbi's work should include a detailed study of his background, but that is beyond the scope of this undertaking. As an anatomist he is a member of the group intermediate between Mundinus and Vesalius, which included such men as Alessandro Benedetti (1460-1525), who succeeded Zerbi at Padua, Alessandro Achillini (1463-1512) of Bologna, discoverer of the malleus, the incus, the labyrinth and the ileo-cecal valve, Berengario da Carpi (1470-1550), who first illustrated an anatomy with drawings from nature, and Marc Antonio della Torre (1481-1512), who was associated with the outstanding artistic and scientific figure of the day, Leonardo da Vinci (1452-1519). Leonicensus (1428-

1524), Linacre (1460-1524), Champier (1472-1539), are among the medical humanists mentioned by Garrison, who flourished during this stirring period of world history that saw the pioneer voyages of the great explorers, the discovery of America, the revival of classic learning, the attacks on scholasticism, the spread of printing and the revolutionary astronomical theory of Copernicus.

Among the many great figures of this day, only one needs special mention, Marsilius Ficinus, the Florentine, noted as the translator of Plato into Italian, and as the head of the academy founded by Cosimo de Medici. He comes into our picture not because of his alleged efforts to rationalize astrology and magic and his supposed opposition to witchcraft, but rather as the author of a work on old age which is widely known and quoted by all writers on the subject. The book, *De triplici vita* (21), is composed of three parts: *De vita sana*, *De vita longa* and *De vita coelitus comparanda*. It was printed at Basel not later than 1498. A German translation, *Medicinarius-Das Buch der Gesundheit*, (22) (Strassburg, 1505), has been read with some difficulty by this writer. In it Ficinus recommends consulting an astrologer every seventh year to find out what the future holds in store. An often quoted counsel of his is to use the medicine of the Magi for old men, pills made of gold, frankincense and myrrh, but he also includes much general advice on hygiene and diet. For a complete study of this scholar the reader is referred to Thorndike's *History of Magic and Experimental Science* (23). As far as can be ascertained Zerbi's book was published before Ficinus'. The latter's wide reknown as a writer on old age is undoubtedly based on his fame as a humanist, rather than on the ground of any original contributions. Although Zerbi's work has left no mark on medical literature, it must have had wide influence in its own day, and may well have been of help to Ficinus.

The sources of Zerbi's views as expressed in *Gerontocomia* are to be found in the writings of great Arab physicians, especially Avicenna (980-1030). In the first book of the *Canon*, one finds abundant and detailed descriptions of old age, as well as full discussions of the regimen. The interested reader will find no difficulty in drawing parallels if he takes the trouble to look up Gruner's excellent translation of Avicenna (24). To appreciate the interest taken in the subject by all the great Arab masters one must turn to the *Care of Old Age and the Preservation of Youth* (25) by Roger Bacon, written in Latin in the thirteenth century and first translated into English in 1683. In it we find references to works on old age and its symptoms by Rhazes, Haly Abbas, Isaac Bemiramis, Averroes, and Johannes Damascenus. The Arabs all emphasize diet, rest, bathing, the use of wine, exercise and mental relaxation in the care of the old. Another widely read medieval work on old age was Arnold of Villanova's *De Conservatione Juentutis et Retardatione Senectutis* (26), a book that combines the point of view of the Moslem School with Arnold's own experience.

In the final evaluation of this work of Zerbi, that seems to have been overlooked for so long, one is justified in concluding that it represents a definite addition to our historical knowledge of the medical aspects of old age. Zerbi, known only as an anatomist, comes alive as a clinician and a sympathetic student of the problems of the old. This review serves also to remind us of the antiquity of some of

our most enlightened attitudes, and fosters the humility that comes only with the study of past centuries and their great thinkers.

The writer is deeply indebted to Dr. Claudius F. Mayer of the Army Medical Library for kindly advice and erudite assistance. Dr. Archibald Malloch and the Staff of the Library of the New York Academy of Medicine have given freely of their time and knowledge to forward this investigation.

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## CONSTRUCTIVE PERICARDITIS. CLASSIC TYPE WITH PERICARDIECTOMY\*

CHARLES K. FRIEDBERG, M.D.

Among the seemingly hopeless cases of intractable and otherwise irremediable congestive heart failure is a group to which surgery offers the hope of great improvement and sometimes of dramatic cure. This group is termed constrictive pericarditis. The possibility of an excellent therapeutic result with the aid of surgery presents an important diagnostic challenge to the physician who must carefully distinguish constrictive pericarditis from congestive heart failure due to a variety of intrinsic cardiac and valvular diseases, from cirrhosis of the liver and from a number of other clinical masquerades under which these cases may be obscured.

The segregation of constrictive pericarditis as an entity is impeded by uncertainty as to its etiology, the absence of a characteristic clinical diagnostic test or of a specific pathologic lesion and disagreement even as to some of the clinical features. Because of these uncertainties there is a danger on the one hand of bringing disrepute on surgical therapy for constrictive pericarditis because of disappointing operative results due to incorrect diagnosis. On the other hand, because of the otherwise hopeless outlook, operation may be warranted in cases which are not entirely characteristic, especially since in many borderline cases the possibility of constrictive pericarditis cannot be excluded. Our knowledge of this condition could be greatly enhanced if we clearly segregated a typical group of cases from those which are atypical, even though there may be operative indications in both groups.

The following is presented as an example of the classic or typical form of constrictive pericarditis.

### CASE REPORT

*History* (Adm. 388710). T. M., a 38 year old laborer, was admitted to The Mount Sinai Hospital on January 10, 1936, because of ascites for one and a half years. In June, 1934, his physician had diagnosed his condition as adhesive pericarditis with a large pericardial effusion and adhesions and a small pleural effusion, on the basis of fluoroscopic and roentgenologic examination. The patient entered another hospital because of dyspnea, orthopnea, weakness and swelling of the ankles. There a diagnosis of rheumatic heart disease and congestive heart failure was made. He subsequently re-entered that hospital because of swelling of the abdomen, dyspnea and edema of the ankles; again a diagnosis of congestive heart failure was made. In May, 1935, he was admitted to a second hospital where 40 ounces of ascitic fluid were removed and a diagnosis of polyserositis or tuberculous peritonitis was made. An exploratory laparotomy was performed, at which time a large hard liver was said to have been found. After leaving that hospital he received injections of salyrgan once a week and was subjected to abdominal paracenteses once a month. In October 1935, he was admitted to a third hospital where, despite abdominal paracenteses, thoracenteses

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\* From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

and the administration of salyrgan, fluid reaccumulated in the serous cavities. A diagnosis of chronic polyserositis was made. He was advised to have a pericardial operation and was transferred to The Mount Sinai Hospital.

There was no significant illness in the patient's past history which might be interpreted as a cause of his disease. While in the Army in 1917 he had had pleurisy. This was characterized by chest pain with only slight fever and no tapping or drainage. He was hospitalized for twelve weeks. Shortly afterward he was discharged from the army apparently well.

*Examination:* The patient was undernourished and pale, while his lips were somewhat cyanotic. The cervical veins were engorged. They became further distended on inspiration. There were signs of fluid over the right pleural cavity and a few râles at the base of the left lung. The heart did not appear enlarged. There were no murmurs. There was no systolic retraction of the chest wall. The abdomen was distended. A fluid wave and shifting dullness were elicited. The liver was enlarged, its free border extending three finger-breadths below the costal margin. There was edema of the lower extremities extending to the thighs and buttocks. There was no paradoxical pulse. The blood pressure was 105 systolic and 85 diastolic.

A diagnosis of constrictive pericarditis was made.

*Laboratory data:* The blood and urine examinations were essentially normal. The venous pressure varied between 19.4 and 23 cm. with a considerable rise on pressure over the right upper quadrant of the abdomen. Circulation time was 26 seconds by the saccharine method (arm-to-tongue time) and 12½ seconds by the ether method. This represented a delay in both the left and right circulations. The vital capacity was diminished (2700 cc.) and the exercise tolerance markedly reduced.

The roentgenologic examination of the chest disclosed a right pleural effusion, elevation of the right diaphragm and thickening of the pleurae of both lungs. The cardiac silhouette was triangular and its left border was sharp and straight, probably due to peripleural adhesions.

The electrocardiogram revealed right axis deviation, isoelectric T<sub>1</sub>, inversion of T<sub>2</sub> and T<sub>3</sub>, with slight depression of the ST segments. There was little or no shift in the electrical axis with change of body position.

*Operations and course:* Because of the long history of recurrent ascites and pleural effusion, and the persistently elevated venous pressure despite rest in bed, restriction of salt and fluids, the administration of diuretics and repeated thoracenteses and paracenteses, pericardiectomy was performed (Dr. H. Neuhof).

At operation the pericardium appeared gray, avascular and about 5 cm. in thickness. The pericardial layers were adherent to each other and to the heart muscle; the pericardial cavity was obliterated. When a large portion of the pericardium overlying the right ventricle had been removed, the heart bulged through the opening in the confining membrane and began to contract vigorously. At the same time the systolic blood pressure, previously between 95 and 105, rose suddenly to 124 and remained at that level postoperatively. Furthermore, the pulse pressure which had varied between 20 and 25 mm. Hg rose above 50 and postoperatively persisted above 40 mm. Hg. However, the venous pressure remained elevated.

After a transient period of improvement postoperatively, there was a recurrence of ascites and pleural effusion despite medical therapy. The temporary incomplete therapeutic effect was attributed to an inadequate removal of the pericardium, especially that overlying the left ventricle. A second operation (Dr. H. Neuhof) was therefore performed on June 5, 1936 and the heart was approached through a left transpleural incision in order to expose the left ventricle. There was no recurrence of adhesions at the previous operative site. A large section of thickened pericardium, about 7.5 x 5.5 cm. in area, was removed from the region of the left ventricle and extending to the diaphragmatic surface. The heart appeared adequately released, as indicated by its herniation through the defect in the resected pericardium and its more vigorous pulsations.

Following a complicated postoperative course and convalescence, clinical improvement

was striking. There was no further recurrence of the serous effusions. The circulation time returned to normal about a month after this second operation, but the venous pressure remained elevated for six months. By December, 1936, the venous pressure was 4 cm. water and there was no rise on abdominal compression. Follow-up examinations for six years have disclosed an almost complete restoration of normal circulatory function. The patient has been gainfully occupied.

#### COMMENT

A presumptive diagnosis of constrictive pericarditis is warranted when there are evidences of right-sided congestive heart failure, especially persistent ascites and pleural effusions, venous engorgement and high venous pressure, in the absence of other known causes of heart disease. These criteria were satisfied in this case. The possibility of earlier diagnosis before this full clinical picture develops is not excluded, but at the present time a case cannot be placed in the category of classic or typical constrictive pericarditis without the complete clinical picture.

The absence of significant cardiac enlargement is a second requirement for the diagnosis of typical constrictive pericarditis. In evaluating the question of cardiac enlargement, it is important to make allowances for the range of normal cardiac size, for the limitations of measuring the size of the heart by palpation and percussion, for the distortion of the cardiac silhouette in roentgenograms because of the elevation of the diaphragm by ascites, and for the width of the thickened pericardium itself. If, however, despite these allowances the heart appears definitely enlarged, there are at least two objections to classifying the case as typical. First, there is the possibility that the heart failure may be due to unrecognized or unrecognizable severe coronary disease with or without antecedent hypertension, to rheumatic heart disease without a valvular lesion or without murmurs, to avitaminosis, to myxedema or to other less common and less easily recognized causes of heart failure. Second, the clinical picture of constrictive pericarditis results from an interference with the inflow of blood into the heart, with the diastolic relaxation of the ventricles, and to a lesser and debatable extent with their systolic contraction. It is difficult to understand why the already enlarged heart should interfere either with an adequate inflow of blood or with an adequate diastolic ventricular volume.

*Hypertension is absent* in the typical form of constrictive pericarditis. In fact, as a rule, the blood pressure is low. The objections to including cases with hypertension in the "typical" category are similar to those enumerated for enlargement of the heart. The presence of hypertension adds an element of uncertainty to the etiology of the heart failure, and the abnormal physiology of constrictive pericarditis is such as to result in a reduced cardiac output and a low blood pressure.

The classic case of constrictive pericarditis not only has a low or low normal systolic pressure, but more strikingly a *low pulse pressure*. This is usually associated with a *diminution or absence of cardiac pulsations* as determined fluoroscopically or by roentgen kymography. These findings are also the result of the diminished cardiac inflow and ventricular diastole, and the resulting

diminution in stroke output. The low pulse pressure and diminished cardiac pulsations are of importance not only in themselves but especially in contrast with the findings after decortication of the constricting pericardium. In the typical case this procedure should be followed by a prompt and striking increase in cardiac pulsations and in pulse pressure. A rise in systolic pressure by itself is less significant if the previous pulse pressure does not increase.

Broadbent's sign, or systolic contraction of the chest wall, often attributed to pericardial adhesion, is actually due to marked cardiac enlargement. Therefore this sign, like enlargement of the heart, excludes a given case from the "typical" category of constrictive pericarditis. On the other hand, a paradoxical pulse and inspiratory expansion of the cervical veins are frequently observed in classic cases of the disease, but these signs may be absent.

Perhaps the most readily apparent and the most striking evidence of typical constrictive pericarditis is the *protrusion or herniation of the strongly contracting ventricle through the defect* in the pericardium created by surgical removal. In its absence, the diagnosis must remain uncertain or at least the case cannot be classified as typical. On the other hand, observation of this phenomenon does not guarantee permanent or complete improvement in the clinical course as noted in the case reported above. Thus, when decortication is followed by increased contraction and herniation of the heart, the diagnosis of typical constrictive pericardium is so definite that failure to obtain permanent improvement suggests incomplete decortication and warrants reoperation.

The postoperative clinical course is one of the less reliable, although greatly emphasized, criteria of the correctness of the diagnosis. In many instances, the preoperative failure to diminish or eliminate the signs of congestive heart failure does not necessarily denote the presence of a mechanical impediment to cardiac function (i.e., a constricting pericardium), but may be due to incomplete bed rest, insufficient restriction of salt and fluids, inadequate digitalization or other shortcomings in the management of congestive heart failure, or to irreversible cardiac damage or perhaps occasionally failure to eliminate the causative factor (e.g., avitaminosis, hypothyroidism, anemia, etc.).

Postoperative improvement without strict preoperative control does not necessarily indicate that the heart failure was due to constrictive pericarditis or that the recovery may be attributed to the operation. The recovery may be due to a stricter and more prolonged period of bed rest than was given before the operation or to a better medical regimen postoperatively. It may also be a coincidence, for occasionally a good clinical result is observed postoperatively when the operative procedure did nothing to warrant any improvement of the circulatory dynamics. Occasionally also, even without operation, ascites which had necessitated repeated abdominal paracenteses, fails to recur for some inexplicable reason.

The pathologic appearance of the excised pericardium cannot be used as the determining factor in classifying a case as typical constrictive pericarditis. As a rule, the pericardium is composed of hyalinized connective tissue with occasional collections of lymphocytes, is relatively avascular and may be calcified.

This appearance is, however, not specific. Furthermore, some authors have described the presence of tubercles and tuberculous granulation tissue in the excised pericardium. Apparently there is no universally accepted pathologic criterion of constrictive pericarditis.

#### SUMMARY

The typical case of constrictive pericarditis is characterized by ascites, pleural effusions, venous engorgement and a high venous pressure which persist despite prolonged and rigid medical therapy for heart failure. There are no evidences of intrinsic cardiac or valvular disease, the heart is normal or small or at least not significantly enlarged, the systolic blood pressure is normal or low, the pulse pressure is diminished and cardiac pulsations hardly noticeable. At operation the pericardium is thickened, avascular and may be calcified and its resection is followed by sharply increased pulsations, bulging of the heart through the pericardial defect and an elevation of systolic and pulse pressure. Postoperatively, adequate decortication is followed by a progressive clinical improvement, but the return of the venous pressure to normal may be delayed for many months.

## CONSTRUCTIVE PERICARDITIS, AN ATYPICAL CASE. EXTREME ASCITES. CURE BY PERICARDIECTOMY\*

WILLIAM HITZIG, M.D.

This case is without dramatic parallel in the history of constrictive pericarditis. It is atypical not only because of the absence of a high venous pressure when the ascites was removed but also because of the operative findings, namely the failure of the heart to herniate through the pericardial gap. It also demonstrates the value of accurate venous pressure measurements and especially the value of the upper abdominal compression maneuver upon the height of the venous pressure as a means of determining the presence of right heart failure. The persistence of a rise in the venous pressure level during right upper abdominal compression even when the initial venous pressure was normal was more significant than any other physical finding or laboratory procedure leading to the diagnosis of constrictive pericarditis.

### CASE REPORT

*History* (Adm. 440376). J. V., a 41 year old woman with a nine year history of frequently recurring ascites for which 150 abdominal paracenteses had been performed was admitted on September 20, 1938. Her sole complaint was recurrent ascites. In 1931 she had an exploratory operation at another hospital where the liver was found to be markedly enlarged, irregular and scarred. On the assumption that this was a Laennec's cirrhosis, a Talma operation was performed. Because the ascites recurred rapidly following each abdominal paracentesis another operation was carried out in 1936. This time an attempt was made to establish a pleuropéritoneal fistula by removing a portion of the left diaphragm. An extensive adhesive pleuritis was encountered. The fistulous communication proved ineffectual and abdominal paracenteses were still necessary at regular intervals. In 1937 she developed marked edema of the face, legs and feet. Intraabdominal malignancy was then suspected and radiotherapy was administered to the abdomen. In July 1938 a sapheno-peritoneostomy was performed without therapeutic effect. Fluid continued to accumulate in the abdomen and she was finally discharged in September 1938 with a diagnosis of atrophic cirrhosis of the liver.

*Examination:* The patient appeared chronically ill. The heart was not enlarged; there were no murmurs; P<sub>2</sub> was louder than A<sub>2</sub>. The liver was firm, sharp-edged and palpable about three inches below the costal margin. There was a fluid wave with shifting dullness in the abdomen. There was no peripheral edema.

*Laboratory data:* The blood pressure was 110 systolic and 80 diastolic. The hemoglobin was 70 per cent. Abdominal paracentesis was performed with the removal of 11,000 cc. of straw-colored fluid the specific gravity of which was 1008. Pneumo-peritoneum revealed a large smooth liver and a large spleen.

*Course:* On admission to the hospital a diagnosis of Laennec's cirrhosis was made. Because the patient's physical status was relatively good for an individual suffering from cirrhosis of the liver for such a long period of time, fibroma of the ovary and intraabdominal tumor were suggested. [These were subsequently excluded by the gynecologist and also by the pathologist who failed to find tumor cells in the ascitic fluid.]

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\* From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

*Circulatory data:* The initial venous pressure which in an antecubital vein was 18.5 cm. rose during right upper abdominal compression to 30+ cm. Comparable measurements were obtained in the external jugular vein where the initial venous pressure was 20 cm. and right upper abdominal compression caused a further rise to 39.25 cm. The saccharin circulation time was 20 seconds. The high initial venous pressure and marked rise on right upper abdominal compression were definitely indicative of right ventricular failure which in view of the history of recurring ascites with 152 abdominal taps, the relative well being of the patient and the finding of adhesive pleuritis at a previous operation suggested the diagnosis of hypodiastolic failure on the basis of constrictive pericarditis. However, when an abdominal paracentesis was performed at this point and 5,000 cc. of fluid was removed, the initial venous pressure with the abdomen empty was only 9 cm. of blood. Compression of the right upper quadrant or left lower quadrant, however, caused an additional rise of 9.5 cm. During the following two days the venous pressure in an antecubital vein was only 8 cm. and 7 cm. respectively but with each measurement abdominal compression caused a further rise of 12 and 12.5 cm. The drop of the initial venous pressure to a normal level seemed to throw doubt on the diagnosis of constrictive pericarditis. It was argued, however, that the lowering of the initial venous pressure was not as important as the effect of right upper abdominal compression since the level of the initial venous pressure in this patient seemed to be dependent upon the absence or presence of ascites. The accuracy of this assumption was subsequently borne out by the following developments. The initial venous pressure rose progressively to 17 cm. and right upper abdominal compression effect became more prominent when the peritoneal fluid reaccumulated. Removal of the ascites was again followed by a drop in the initial venous pressure. That the presence or absence of ascites determined the height of the initial venous pressure by redistributing the circulating blood volume in the splanchnic blood depots was finally established in this patient by using an inflated rubber bag (to mimic the ascites) and noting the effect of abdominal compression upon the height of the initial venous pressure in an antecubital vein. When the abdomen was empty the initial venous pressure was 9.5 cm. but when the inflated rubber bag compressed the abdomen as in the technique for intravenous pyelography the venous pressure was found to be 27.5 cm.

A roentgenogram of the chest showed elevation of both leaves of the diaphragm. The heart was markedly widened at the base and its borders were irregular, as in cases of extensive pericardial adhesions. With change in position of the patient there was no change in position of the heart. Pulsations over the lower left contour of the heart were diminished. There was relatively little change in the density of the pulsations as observed kymographically. An electrocardiogram showed regular sinus rhythm, tendency to left ventricular preponderance; P waves wide and notches; R-T transition depressed in lead I, T<sub>2</sub> flat, T<sub>3</sub> inverted, T<sub>4</sub> semi-inverted. An electrocardiogram taken in left and right recumbent positions showed only very slight changes in the electrical axis.

During the period of study, the patient received enormous doses of digitalis, mercupurin, ammonium chloride and vitamin B. Despite this therapy, administered on the possibility of lesions other than constrictive pericarditis as the cause of the ascites, the patient continued to gain in weight. Thus, despite atypical features, the foregoing observations, the presence of venous hypertension (during ascites), the absence of significant enlargement of the heart, the roentgenographic features, and the well being of the patient over a long period of time, justified the diagnosis of constrictive pericarditis. It was realized, however, that if the diagnosis was correct, the case was unique. An exploratory operation appeared warranted since there had been no relief from ascites over a long period. Because of the atypical venous pressures and the prominence of the ascites, a block of the inferior vena cava was postulated.

*Operation* (Dr. H. Neuhof, December 6, 1938). For the last mentioned reason a right-sided approach was made to the right lateral aspect of the heart. The pericardium was found to be thickened and immobile. The surface of the heart was widely freed, especially in the region of the inferior vena cava. However, the heart did not escape into the gap

in the dramatic manner ordinarily observed, but it rather appeared in the gap protruding progressively during the remainder of the operation. The release of the heart was completed by excision of the thickened pericardium down to the diaphragm, upward to expose the region of the right auricle and mesially well across the midline. With the patient tilted over toward the left side, the freed inferior vena cava could be seen.

*Postoperative course:* This was complicated by a hemorrhagic pleural effusion treated by thoracentesis. There was slow reaccumulation of ascites. Following the operation the venous pressure was 6 cm., but on right upper abdominal compression there was still a rise to 16 cm. Three weeks after operation the venous pressure was 7.5 cm., but when the abdomen was compressed it rose to 23 cm. Because of these venous pressure measurements and the reaccumulating ascites, the persistence of a constricting factor around the heart was postulated. The patient was discharged unimproved.

The patient was re-admitted on May 13, 1939. Since discharge from the hospital ascites had reaccumulated as before operation and repeated abdominal paracenteses had been performed. The circulatory measurements now were about the same as during the first admission.

*Second operation* (Dr. H. Neuhof, May 19, 1939). A left-sided transpleural approach was made. The excision of the thickened and adherent pericardium over the left heart was carried out. Toward the right side of the exposure the parietal pericardium was especially thickened with plaque-like formation.

*Postoperative course:* There was slow accumulation of ascites and after four weeks a paracentesis was done. Following this the patient was discharged to be followed-up in the Out-Patient Department. There was further slow reaccumulation of some peritoneal fluid but this slowly subsided after a period of several months. There have been no other paracenteses.

During her entire illness the patient had had 176 abdominal paracenteses. At the present time there is no definite evidence of ascites. The veins in the neck are not visibly distended and it should be emphasized that no abdominal paracenteses have been performed since discharge from the hospital in 1939. It is of interest to note that the patient was operated upon in 1941 for acute appendicitis and that ascites was not present at that time.

## ACUTE METASTATIC SUPPURATIVE PERICARDITIS

### TWO-STAGE PERICARDIOSTOMY WITH RECOVERY\*

IRWIN PAUL TRAIN, M.D.

During the past twelve years, the diagnosis of acute suppurative pericarditis as an operative lesion was made in ten patients on the surgical service of Dr. Neuhoﬀ and all were subjected to operation. An analysis of these operative cases disclosed that all had developed as a secondary process in one of two ways: by septic metastasis from a distant primary focus, and by direct invasion from a contiguous or adjacent primary focus. The cases therefore have been classified as metastatic or contiguous pericarditis.

Although improvement in the general condition after pericardiostomy was noted in all ten patients complete recovery occurred in only two cases, one in each group. The recovery in the metastatic pericarditis group took place in a twelve year old boy.

This case is interesting not only because of the recovery in a disease that is characterized by high mortality, but also because it presents several interesting technical features.

#### CASE REPORTS

*History:* (Adm. 397504). At the age of six years the patient sustained an abrasion on his right knee which healed promptly. Three days later there developed the clinical evidence of an acute fulminating sepsis with osteomyelitis of the left humerus. The lesion was drained and staphylococcus aureus was recovered on culture. Staphylococcus antitoxin and repeated transfusions were administered. Sepsis continued and metastatic foci appeared in the left mandible, lungs and soft parts. Ten days after the onset of the illness evidence of cardiac embarrassment appeared, and rapidly became worse. Eight days later clinical and roentgenological evidence of a huge pericardial effusion developed, accompanied by the alarming syndrome of cardiac tamponade.

When the patient was seen as an emergency case in another institution, the child appeared moribund. Pericardiocentesis confirmed the presence of pus within the pericardial sac and pericardiostomy was planned. The general condition was so poor it was believed that anything more than minimal surgery at that time would be disastrous. It was therefore decided to drain the pericardial infection in two stages: the first stage, to be done immediately, was to achieve a rapid decompression of the pericardial sac and eliminate cardiac tamponade; the second stage, to be done at a later time if the patient survived, was to provide a wider exposure of the heart by revision of the pericardial opening.

*Operation* (Dr. H. Neuhoﬀ). Under local anesthesia, an interior subcostal incision was made and the pericardial sac opened. Ten ounces of thick pus under great tension escaped. On culture, staphylococcus aureus grew out. Immediately after the release of tension, the patient's general condition improved. Metastatic foci continued to appear in the soft tissues and bones, each requiring drainage. Five weeks later, the general condition was greatly improved and the patient was transferred to The Mount Sinai Hospital for a definitive operation on the infected pericardium.

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*Second operation* (Dr. H. Neuhof). Under basal avertin supplemented by gas-oxygen anesthesia, the pericardial opening was widely enlarged. It was interesting to note that at this time, the pericardial sac still contained two ounces of thick pus and many pockets of thick purulent exudate.

*Course:* Following the second procedure, both local and general conditions improved more rapidly. The pericardial infection slowly but progressively subsided. Drainage was aided by gentle irrigations and aspirations and the pericardial opening was prevented from closing prematurely by mechanical measures.

Five weeks after the second stage the pericardial infection had cleared completely and the wound was permitted to close. Interval roentgenograms had revealed progressive diminution of the pericardial enlargement. The septic state, in the meantime, had diminished in severity but persisted as a chronic process over a longer period of time, invading new areas of soft tissue and bone. Seven weeks after the second stage the child's general condition had so improved that he was discharged from the hospital.

Since then, the pericardial lesion has remained healed and no cardiac abnormalities have appeared. Although in good general health, afebrile, and negative blood cultures, the patient developed, at intervals, small abscesses in the soft tissues, and bones. Evidently the septic process was still active to some extent despite the use of the sulfonamides within the past two years.

*Comment:* This case, as well as the other nine operative cases referred to previously, thus illustrates that the pericardial infection is only an incidental feature in the clinical picture as a whole. Complete recovery, therefore, depends not only upon the control of the pericardial lesion but also upon the control of the primary or underlying pathologic process.

#### CONCLUSIONS

1. Acute suppurative pericarditis occurs more frequently than is generally believed.

2. It is easily overlooked.

3. It develops usually as a secondary process by septic metastasis or contiguous invasion.

4. Early diagnosis is essential to avoid cardiac tamponade. Pericardiocentesis is the only direct means of establishing the diagnosis and should be performed in all suspected cases before the pericardial sac becomes tensely distended with pus. It should be remembered that clinical and roentgenologic evidence of pericardial effusion is present only after a considerable quantity of purulent fluid has collected within the pericardium.

5. Pericardiostomy should be performed promptly at the most dependent site of the pericardial sac. The anterior subcostal approach appears to be satisfactory. In extremely poor risks, a two-stage procedure may be of value.

6. Recovery depends upon the control of the underlying pathologic process as well as of the pericardial infection. Acute suppurative pericarditis often plays only an incidental rôle in the clinical picture.

## PATENT DUCTUS ARTERIOSUS; LIGATION\*

ERNEST E. ARNHEIM, M.D.

*History* (Adm. 487369). A girl, aged 11 years, was admitted to The Mount Sinai Hospital on March 26, 1942. The patient was well, except for scarlet fever, until six years before admission, when she was hospitalized because of fever and joint pains. At that time a systolic precordial murmur was heard. Roentgen examination of the chest revealed "slight prominence of the conus". A diagnosis of rheumatic heart disease and mitral insufficiency was made. Hospitalization for eight days was followed by bed-rest at home for one month. Thereafter, the mother noted that the child tired easily and complained of dyspnea on exertion. In addition, there were intermittent attacks of joint pains, sore throat, fever, and chills necessitating hospital care. During the past few years the mother noted occasional swelling of the ankles. A few months before admission a blood culture was reported sterile. Roentgen examination of the chest at that time showed evidences of pulmonary congestion.

*Examination:* The important features of the examination were confined to the heart. There was a loud "machinery" murmur over the precordium best heard at the pulmonic area, and a systolic blow of lower pitch at the apex. A thrill was felt over the precordium most prominently at the base. The pulse rate was 88. On admission the blood pressure was 104 systolic and 70 diastolic in both arms. On a subsequent examination the blood pressure was 112 systolic and 68 diastolic; after exercise this changed to 126 systolic and 52 diastolic. The venous pressure was 10.5 cm.

*Laboratory data:* Blood: sedimentation time, over three hours; hemoglobin, 78 per cent; leucocytes 16,000, with 72 per cent polymorphonuclear leucocytes. Urine: occasional white blood cell and red blood cell on microscopic examination.

Roentgen examination of the chest, including fluoroscopy, revealed a pronounced exaggeration of the pulmonary segment on the left cardiac contour; the lungs were normal. The electrocardiogram showed no abnormal findings. A phonocardiogram revealed a systolic and diastolic murmur present at all valve areas becoming continuous at the pulmonic area. Studies of the heart and great vessels by angiocardiography showed moderate dilatation of the left ventricle; the aorta was normal except for a local dilatation in the portion distal to the isthmus.

*Operation* (Dr. E. E. Arnheim, April 7, 1942). Under cyclopropane anesthesia, the site of the ductus arteriosus was exposed through a left submammary incision. The ductus arteriosus was about 10 mm. long and 8 mm. in diameter, the thickness of a large vein. After isolation of the ductus, particularly on its posterior surface, a double ligature of heavy braided silk was drawn around the ductus and tied snugly, but not tightly, on the aortic side. An additional single ligature, of the same material, was tied tightly on the pulmonic side. After the latter ligature was tied there was disappearance of the thrill in the pulmonary artery. For purposes of future visualization, two metal clips were attached to the ligature on the aortic side and one metal clip to the ligature on the pulmonic side.

*Course:* The highest postoperative temperature was 100.6°F. The precordial murmurs

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and thrill were absent. The wound healed by primary union. The patient was discharged in excellent condition fifteen days after operation.

Examination seven weeks after operation showed the heart to be negative. The blood pressure was 100 systolic and 76 diastolic. An angiogram showed the dilatation of the aorta distal to the isthmus to be less fusiform, more sharply localized, and the bulge more exaggerated. The phonocardiogram confirmed the absence of cardiac murmurs. The general condition of the child was excellent.

SUBACUTE STREPTOCOCCUS VIRIDANS ENDARTERITIS SUPER-  
IMPOSED ON PATENT DUCTUS ARTERIOSUS. RECURRENCE  
AFTER 12½ YEARS. RECOVERY FOLLOWING OPERATIVE  
TREATMENT<sup>1</sup>

ARTHUR S. W. TOUROFF, M.D.

CASE REPORT

*History* (Adm. 477596). G. O., a female, aged 51 years, was admitted to The Mount Sinai Hospital on August 12, 1941. During early adult life a murmur, which was attributed to a congenital cardiac anomaly, was discovered. The past history was irrelevant otherwise until 12½ years before admission at which time she developed fever, malaise and lassitude. At first the diagnosis of grippe was entertained but when the symptoms persisted and chills supervened, she was admitted to a hospital for investigation. There blood cultures were found to be positive for streptococcus viridans and the diagnosis of "subacute bacterial endocarditis engrafted upon a congenital cardiac anomaly" was made. Treatment consisted of repeated transfusions and injections of an autogenous vaccine prepared from organisms recovered from the patient's blood. After an illness of approximately 1½ years, during which she developed characteristic evidences of subacute bacterial endocarditis consisting of repeated crops of petechiae, enlargement of the spleen, pulmonary and renal infarction, irregular fever and chills, she recovered.

From that time until her admission to The Mount Sinai Hospital, she suffered only from mild circulatory failure characterized by dyspnea on moderate exertion, orthopnea and slight cough, all of which increased slowly but progressively.

The present illness began approximately 4½ weeks before admission, and consisted of weakness and mild fever. These symptoms continued until five days before admission, when she suffered a severe attack of pain in the left chest associated with cough and blood-streaked sputum. Concomitantly the temperature rose to 105° F. and she was admitted to this Hospital.

*Examination.* On admission the temperature was 101.4°F. and the pulse rate was 96 per minute. Dyspnea and orthopnea were present. The significant physical findings were confined to the heart where a loud "machinery" murmur was heard over the pulmonic area throughout systole and most of diastole. The blood pressure was 105 systolic and 60 diastolic. Examination of the lungs disclosed impaired resonance, diminution of breath sounds and the presence of râles at the left base posteriorly.

*Laboratory data.* X-ray examination of the chest revealed enlargement of the heart to the left, a prominent pulmonic conus and moderate pulmonary vascular congestion. Blood count and urine were normal. A blood culture revealed 40 colonies of streptococcus viridans per cc. On the basis of the foregoing studies, the diagnosis of patent ductus arteriosus complicated by subacute streptococcus viridans endarteritis was made.

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<sup>1</sup> From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

*Course.* In spite of the administration of sulfapyridine and sulfathiazole, there was only temporary regression of fever. A blood culture performed thirteen days after admission, disclosed 52 colonies of organisms per cc. By the nineteenth day, profound secondary anemia and progressive physical deterioration had supervened. These features, together with the lack of response to chemotherapy, led to the decision to proceed with operation.

Operation, consisting of double ligation of the patent ductus arteriosus, was performed on September 4, 1941 (Dr. Arthur S. W. Touroff). The first postoperative blood culture, performed forty minutes after operation, was sterile. Additional blood cultures were taken on the second, fourth, ninth and twelfth postoperative days, and these also were sterile. The postoperative course was relatively uneventful, the patient being discharged on the thirteenth day after operation. No chemotherapy was administered at any time during the postoperative period.

Approximately nine months have elapsed since operation. During this period, the patient has remained entirely free of symptoms of infection and circulatory failure.

#### COMMENT

This is the second case of spontaneous recovery from subacute bacterial endarteritis superimposed on patent ductus arteriosus to be recorded. It is also the first case of infected patent ductus arteriosus in which infection recurred after the patient recovered from an initial attack. Finally this patient is one of a personal series of twelve with infected patent ductus arteriosus, seven of whom recovered from infection following operation.

# MASSIVE PULMONARY EMBOLISM; CONTINUOUS INTRAVENOUS MORPHINE DRIP; RECOVERY<sup>1</sup>

HAROLD NEUHOF, M.D.

## CASE REPORT

*History* (Adm. 472822). W. C., 30 years old, had had a chronic cough and copious expectoration of pus for 27 years. There had been occasional hemoptyses and occasional foul sputum. Bronchoscopy and bronchography demonstrated pronounced bronchiectasis which was limited to the left lower lobe. On May 13, 1941 this lobe was removed by individual ligation of vessels and bronchus. The operation was without incident and the postoperative course was uneventful and essentially afebrile.

Eleven days after operation, on the morning of May 24, the patient became apprehensive and, shortly after, there was the abrupt onset of substernal oppression, severe dyspnea, and collapse. Respirations were 56, the pulse was small and rapid, the color a combination of cyanosis and pallor. A profuse sweat appeared. The wound was examined and found to be free from infection. Oxygen was administered. A large dose of morphine was given which was followed immediately by the continuous intravenous administration of morphine (dosage to be noted later). In the afternoon respirations were 46, there was persistent pallor and collapse. The pulse was 120 and small. The patient was kept under close observation with special reference to an optimal time for proceeding with embolectomy. At 6 p.m. the color was poor. The respirations were 46 and labored, the pulse was very rapid and small. At this time the impression was gained that death would probably ensue. Thus embolectomy appeared indicated according to the experiences of those who have had successful results. However, the decision was reached to continue with conservative treatment. The morphine drip was continued. The next day the cyanosis was slightly less, but severe dyspnea and tachycardia were maintained. An hemoptysis indicated the presence of infarction, presumably because of detachment of a fragment from the pulmonary embolus. It was noteworthy that there was no longer any anxiety on the part of the patient and that there was complete freedom from pain. The patient's condition of well-being referable to the continuous administration of morphine was in striking contrast to the obviously critical clinical state. The latter persisted for the next two days. Thereafter there was progressive improvement. On May 29, that is five days after the onset of the clinical manifestations of embolism, convalescence set in.

The amount of morphine which was administered daily for the period of five days ranged between  $1\frac{1}{2}$  and  $1\frac{3}{4}$  grains. Throughout this period the state of well-being was maintained uniformly. At no time was there any evidence of morphinism and the rapid respiratory rate which persisted throughout the severe phase of the clinical picture of embolism was apparently uninfluenced by the amount of morphine which was administered.

## COMMENT

Although recovery cannot be ascribed in this case to morphine the continuous administration of the drug obviously played an important role. The method

<sup>1</sup> From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

of administering morphine as a continuous drip, first described in 1941<sup>2</sup> offers a number of advantages not enjoyed by the customary interrupted administration of the drug.

<sup>2</sup>Neuhof, H.: The Continuous Intravenous Administration of Morphine After Operation, *J. Mt. Sinai Hosp.* 7: 601, 1941.

## NON-LUETIC AORTIC ANEURYSM—ANGIOCARDIOGRAPHIC DIAGNOSIS<sup>1</sup>

M. F. STEINBERG, M.D., A. GRISHMAN, M.D., AND  
M. L. SUSSMAN, M.D.

A precise diagnosis of any mediastinal mass is essential in order to determine the correct therapeutic procedure. The case to be presented illustrates some of the diagnostic difficulties, the importance of complete study, the value of angiocardiology and finally, the therapy in an unusual aortic aneurysm.

### CASE REPORT

*History* (Adm. 481565). F. M., a 31 year old white housewife, had complained of a dry cough for three weeks. She visited her physician who discovered a mediastinal mass on fluoroscopic examination. Upon his advice, the patient was admitted to the Surgical Service of Dr. Neuhof for study and treatment.

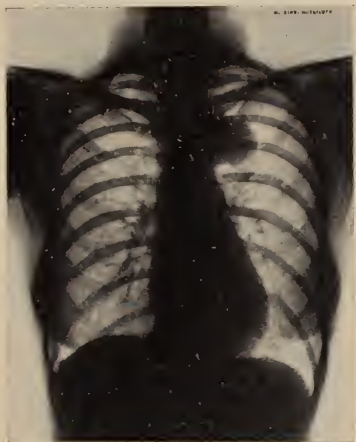


FIG. 1. Conventional postero-anterior film showing bilocular mass to the left of the vascular pedicle

*Examination:* The following significant positive findings were elicited: A left infra-clavicular bruit synchronous with the pulse and a difference in the blood pressure in the upper extremities, right arm 120 systolic and 68 diastolic, left arm 90 systolic and 70

<sup>1</sup> From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.



FIG. 2. Angiocardiogram, right anterior oblique position. Seven seconds after the beginning of the injection, the bilocular mass is opacified indicating its vascular origin.



FIG. 3 (Courtesy X-ray Department, Presbyterian Hospital, New York). Conventional postero-anterior film following the wiring operation. The location of the wire within the locules is demonstrated. A few strands are also seen in the lumen of the descending aorta.

diastolic. The Wassermann test was reported negative. Roentgenogram of the chest revealed a bilocular mass to the left of the superior mediastinum (fig. 1). In the lateral projection, it was seen in the middle mediastinum. Fluoroscopy was reported as revealing pulsation of the mass in a lateral direction only, indicating that the pulsation was transmitted rather than expansile. Kymographic studies were inconclusive.

*Course.* On the basis of the above findings, a clinical diagnosis of mediastinal tumor, possibly a dermoid cyst, was made.

Exploratory thoracotomy by Dr. Neuhoof, revealed a bilocular aneurysm of the aorta at the junction of the ascendens and arch. A thrill was felt over one of the locules.

Angiocardiography was performed postoperatively. In the right anterior oblique position the bilocular aneurysm was opacified seven seconds after the rapid intravenous injection of 70 per cent Diodrast (Winthrop) (fig. 2). The diagnosis of aneurysm of the aorta could have been established preoperatively beyond any doubt by this procedure.

The exact etiologic basis of the aneurysm was conjectural. However, because of the patient's youth, the absence of a luetic history and the negative Wassermann reaction, it was felt that it was congenital and not luetic.

Transferred from The Mount Sinai Hospital, the patient entered the Presbyterian Hospital, New York City, where Dr. Blakemore wired and electro-coagulated the aneurysm in two stages. Postoperative roentgenograms demonstrated the location of the wire within both locules of the aneurysm (fig. 3), and direct injection of Diodrast 70 per cent into the aneurysm revealed clot formation within the lumen.

The patient is well and asymptomatic at present.

#### COMMENT

Erroneous diagnosis of mediastinal tumor resulting in exploratory operation might be avoided in most instances if the following precautions are observed:

1. All mediastinal masses in the region of the vascular pedicle should be studied completely before operative intervention is decided upon.

2. Fluoroscopic and kymographic studies do not always aid in differentiating mediastinal tumor from aneurysm. Angiocardiography should be performed in all instances where there is a reasonable doubt in the differential diagnosis between mediastinal tumor and aneurysm.

3. A positive angiocardiographic finding is of much more significance than a negative one. Clot formation and excessive dilution of the diodrast blood mixture may be causes of non-opacification of the aneurysm.

## MULTIPLE ANEURYSMS OF INDETERMINATE ORIGIN. ARTERIAL REPAIR<sup>1</sup>

OLON S. BERNSTEIN, M.D.

### CASE REPORT

*History* (Adm. 415841). A. F., a 45 year old Swedish elevator operator had several incisions for "tuberculous" cervical adenitis in early youth and two episodes of "rheumatic fever," the first at 14, the second at 40 years. A peptic ulcer accompanied with severe pain and bleeding appeared two years before admission, yielding readily to dietary control. He denied venereal infection and many Wassermann tests had been negative.

In 1929 the sudden appearance of a painful tender swelling in the calf of the right leg accompanied by fever and leucocytosis was interpreted as an abscess but aspiration at the Lutheran Hospital disclosed blood which rapidly clotted. After a month's observation, during which fever persisted and there was evidence of thrombophlebitis of the veins of the lower calf, a large dissecting aneurysm of the posterior tibial artery was exposed at operation and excised. The specimen disclosed "a thickened media with some hyaline and myxomatous degeneration." The pathologic picture was interpreted as arteriosclerosis with a beginning dissecting aneurysm. The Wassermann reaction remained negative after provocative arsenicals.

The patient was free from discomfort for eight years (until September 1937) when, following intermittent right lumbar pain of two months' duration, the right leg became easily fatigued and constant dull pain appeared in the right popliteal space. The pain increased in severity and walking became impossible. He was admitted to The Mount Sinai Hospital.

*Examination.* A pulsating walnut-sized mass in the right popliteal space was recognized as an aneurysm of the popliteal artery. The blood pressure was 140 to 160 systolic, 100 to 106 diastolic. There were no abnormalities in circulation or circulation time. A lymphangitic and thrombophlebitic process of the inner aspect of the right leg was associated with fever ranging to 102°F. for a period of two weeks. The blood pressure rose to 174 systolic and 108 diastolic.

*Course:* With evidence of rupture of the aneurysm, hemorrhage into the soft parts, and impaired circulation in the right leg, an obliteration aneurysmorrhaphy was performed (Dr. H. Neuhoef). A huge false aneurysm was opened and old and recent blood clots evacuated. After considerable search the orifices of the popliteal artery were found and shut off. In the light of the preoperative infection drainage was employed. There was a moderate fall in blood pressure after operation. Recovery was complicated by bleeding from the wound which required revision. The roentgenogram of the heart disclosed considerable enlargement with concentric hypertrophy. Histologic study of a small portion of the aneurysmal wall did not disclose any evidence of syphilis.

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<sup>1</sup> From the Surgical Service of Dr. Harold Neuhoef. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

*Second admission.* (September 20, 1941). The patient was well until ten days before admission when he suddenly experienced severe lancinating pain in the right side of the neck and face which was followed within a few hours by hoarseness. Because of increase in the symptoms he was readmitted to the Hospital.

A chest roentgenogram disclosed a shadow in the upper portion of the right pulmonary field which appeared characteristic of a substernal thyroid. The paralysis of the right vocal cord was considered unusual in this type of tumor. An exploration disclosed a normal thyroid gland and a mass measuring 2 x 1 cm. within the substance of the scalenus just above the superior thoracic aperture. The mass was hard, apparently intimately identified with the subclavian vessels and was interpreted as a malignant tumor, probably vascular in type. The patient was discharged from the hospital October 5, 1941.

*Third admission* (February, 1942). On reviewing the history of the preceding aneurysms, the character, location and vascularity of the mass, the possibility of a manifestation of the same disease arose, and the patient was again admitted for re-exploration. Studies with Diodrast were not conclusive for aneurysm. Through an anterior transmediastinal approach the innominate artery was exposed and traced upward to its point of bifurcation at which point a tumor was found that lay between the right common carotid and the right subclavian arteries and partially behind these vessels. The mass was smooth, encapsulated, pulsated freely but was not expansile. On aspiration blood was readily obtained, confirming the impression of aneurysm. The failure of Diodrast to demonstrate the aneurysm was not adequately explained and was undoubtedly misleading at the first operation. As the removal of the mass would have necessitated ligation of the common carotid, it was deemed unwise to proceed.

The succession of aneurysms in the posterior tibial, popliteal, and now at the bifurcation of the innominate artery suggested the presence of an obscure, disseminated vascular disease. For this reason a biopsy of a segment of the right ulnar artery was performed, which disclosed "focal medial calcification and arteriosclerosis."

#### COMMENT

A degree of arteriosclerosis perhaps disproportionate to the patient's age is indicated by the histologic picture of moderate medial calcification and roentgen evidence of vascular calcification as disclosed in the films of the extremities. Idiopathic disease of the arteries similar to the frequently described "temporal arteritis" and the giant cell chronic arteritis described by Gilmour must also be considered. In any event the evidence is clear in this case that the disease does not interfere with the operative repair of aneurysms in the peripheral arteries. Not only has healing been adequate but also the absence of recurrence after operative repair is noteworthy.

# TRAUMATIC POPLITEAL ANEURYSM. OBLITERATIVE ENDO-ANEURYSMORRHAPHY. END RESULT<sup>1</sup>

GABRIEL P. SELEY, M.D.

## CASE REPORT

*History.* The patient, an adult male, was first admitted to The Mount Sinai on July 24, 1924, complaining of pain in the left foot and leg of seven days duration and swelling of the popliteal region for six years.

Six years prior to admission he suffered a through and through war wound (bullet) of the left knee. Swelling appeared some time later but the patient remained symptom-free. Seven days before admission, while walking, he was seized with severe pain in the left calf which spread to involve the foot and toe. Bluish discoloration of several toes was noted.

*Examination.* The left leg was mottled, purplish-red, three toes were blue and cold and ulcerations were present at their tips. Weak pulsations could be felt in the dorsalis pedis and anterior tibial arteries. In the left popliteal region there was an irregular oval pulsating mass 5 x 3 inches in diameter.

*Operation* (Dr. H. Neuhof). Immediate operation was performed under ether anesthesia. A fusiform sac was encountered overlain by branches of the popliteal nerve. It was entered and a large lamellated adherent thrombus evacuated. The mouths of entry and exit of the popliteal artery were shut off from within, the excess sac wall ablated, and the aneurysm obliterated by tier sutures.

*Course.* The postoperative course was satisfactory. Gangrene of the tips of the first three toes was present on discharge from the hospital. The patient was readmitted two weeks later for partial excision of the three toes.

*Follow-up.* Six months after operation the patient could walk several miles without discomfort. Two years later there were no symptoms or recurrence of swelling. In 1940 he was again admitted for an appendectomy. Measurements at the calf and ankle made at this time showed no difference between the two sides. Oscillometric readings showed slight diminution at the left calf. It is now eighteen years since the operation and the patient is completely symptom-free. Thus, complete obliteration of the aneurysm by endo-aneurysmorrhaphy afforded a perfect functional result.

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<sup>1</sup> From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

# INFECTED TRAUMATIC FEMORAL ARTERIOVENOUS ANEURYSM. PROLONGED STREPTOCOCCUS VIRIDANS BACTEREMIA. EXCISION. CURE<sup>1</sup>

I. G. KROOP, M.D.

Bacterial endophlebitis occurring in an acquired arteriovenous fistula usually leads to a chronic fatal septicemia as is seen in subacute bacterial endocarditis. In both instances, chemotherapy is as yet of no avail in the permanent sterilization of the blood stream. The persistence of an endovascular bacterial focus which constantly feeds organisms into the blood stream is the reason for this failure. In acquired infected arteriovenous fistula or aneurysm, the endovascular focus is usually accessible to surgical treatment because the aneurysm is a result of a penetrating trauma to a peripheral artery and vein. It is important, before excision is contemplated, to be reasonably certain that there has been no secondary localization of bacteria on other endothelial surfaces. Thus, operation is contraindicated in mycotic arteriovenous aneurysm during the course of subacute bacterial endocarditis, unless there is danger of rupture and death from exsanguination. It is likewise contraindicated in infected traumatic arteriovenous aneurysm where there is secondary localization on the heart valves.

The case to be presented fully reported elsewhere (1) is the second instance of cure of subacute bacterial septicemia following excision of an infected arteriovenous aneurysm, the first being reported by Hamman and Rienhoff in 1935 (2).

## CASE REPORT

*History.* The patient, a man aged 26, without any history of congenital or rheumatic heart disease, nine years before admission suffered a through-and-through gunshot wound of the left thigh. One year after the injury, there was evidence of cardiac decompensation resulting from the circulatory effects of an arteriovenous aneurysm, with symptoms of easy fatigue, dyspnea on exertion, and palpitation. Seven years after the original injury, symptoms of sepsis began following extraction of a tooth and dental reparative work. Chills, sweats, fever to 103°F., anorexia, weight loss, and weakness, with episodes of pleuritic pain and cough, continued for two years, being uninfluenced by sulfanilamide and sulfapyridine.

*Examination.* Clinical and laboratory investigations pointed to a chronic sepsis maintained by an infected arteriovenous aneurysm. Repeated blood cultures revealed streptococcus viridans. There was no evidence of old or recent valvular involvement and no peripheral embolic manifestations.

*Operation.* An infected arteriovenous aneurysm was excised (Dr. A. S. W. Touroff). The pathologist reported "An arteriovenous aneurysm showing subacute bacterial endovascularitis, numerous Gram-positive cocci being found within the vegetations."

*Course:* Convalescence was uneventful with negative blood cultures, gain in weight, and disappearance of all symptoms of cardiac insufficiency and sepsis.

Nine days after discharge from the hospital the patient was again admitted because of

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<sup>1</sup> From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

abdominal pain, diarrhea, fever, and splenomegaly. After an eight day period of study which failed to reveal the cause of fever, the old operative site was explored for the possibility of residual thrombophlebitis despite negative blood cultures. The common femoral, the upper portion of the superficial femoral, and stump of the deep femoral vein were excised as a precautionary measure. The pathologist could find no evidence of thrombophlebitis. Following operation recovery ensued rapidly. Fifteen months have elapsed and the patient remains entirely well.

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## MALIGNANT HYPERTENSION—TWO AND ONE-HALF YEARS AFTER OPERATION<sup>1</sup>

HENRY DOLGER, M.D.

### CASE REPORT

*History* (Adm. 453067). A forty year old female physician was admitted to the hospital on February 16, 1940. She had had erythema nodosum at 22, and scarlet fever at 28 years of age. The latter was followed by a two day period of albuminuria without other manifestations of nephritis. In 1939 she was admitted to the gynecological service for investigation of metrorrhagia on a functional basis, and at that time hypertension was first noted, the blood pressure being 210 systolic and 110 diastolic. There were no symptoms referable to the hypertension then.

On this admission she complained of frontal and temporal headache, vertigo, morning nausea, failing memory, impaired mental faculties, extreme nervousness and depression of one year's duration. For six weeks prior to admission she had noted the onset of dyspnea, palpitation, and substernal oppression on exertion, intermittent ankle edema, and nocturia. The precordial pain was intense, and radiated through to the back. She was forced to abandon her medical work, being completely incapacitated.

*Examination.* The patient was a well developed and well nourished woman. There was moderate exophthalmos and myopia. The fundi revealed irregular narrowing of the "silver wire" arteries with definite arteriovenous compression, but no exudates or hemorrhages. The heart was enlarged to the left with blowing systolic murmurs being present at both apex and base, in addition to an accentuated ringing aortic second sound. There was moderate sclerosis of the radial arteries. The blood pressure was 220 systolic and 120 diastolic. The liver edge was not palpable. There was no cyanosis, and edema of the ankles was slight. The patient was depressed, anxious, and agitated.

*Laboratory data.* The maximum urinary concentration was 1.020, and there was one plus albuminuria with a small number of hyaline casts. The blood urea nitrogen, venous pressure, saccharin time and phenosulphophthalein excretion were all normal. The electrocardiogram revealed no evidence of myocardial damage.

*Operation* (Dr. H. Neuhof). A right thoracic splanchnicectomy was performed, the main splanchnic trunk being excised extrapleurally. Because of a rent in the pleura made during the dissection of the trunk, the patient developed a hemopneumothorax postoperatively. There was a stormy postoperative course which subsided after the aspiration of fluid and air. Immediately following operation the blood pressure fell to extremely low levels but within twenty-four hours it had risen to 114 systolic and 64 diastolic. It rose gradually during the postoperative period to levels around those obtained on admission.

Three weeks later the left side was subjected to the splanchnicectomy. The main splanchnic trunk was exposed and the the dissection was carried down across the diaphragm to include the left semilunar ganglion. Postoperatively the blood pressure fell to 90 systolic and 50 diastolic, but the general condition was excellent. By the second week the

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<sup>1</sup> From the Surgical Service of Dr. Harold Neuhof. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

blood pressure had risen to 160 systolic and 100 diastolic. The patient was then permitted out of bed, and when discharged on the third week after the second stage, the blood pressure was 180 systolic and 110 diastolic.

*Course.* Since operation the blood pressure has persistently remained high, yet there is the most striking improvement both subjectively and objectively. Immediately following the first stage there was noted the complete disappearance of headache, nausea, and vertigo. After leaving the hospital there was complete recovery of capacity for work. The patient undertook an arduous medical position which demanded unusually long hours (sixteen consecutive hours of work every other day). Despite such a strenuous program she feels completely asymptomatic. She has had no further precordial distress or dyspnea. The insufferable insomnia has completely disappeared. The impaired memory, the dulled mental faculties, the nervousness and anxiety have also disappeared. The fundi reveal no change in the arteries but there is no longer any arteriovenous compression. Albuminuria has also disappeared.

#### COMMENT

Although there has been no significant reduction in blood pressure, there can be no doubt that the operation was successful in arresting the acceleration of the malignant phase of essential hypertension in this patient. The literature affords no explanation for the discrepancy between the unaltered blood pressure postoperatively and the striking amelioration of the accompanying symptoms and signs. The remarkable clinical improvement evident in patients subjected to this procedure warrants more widespread application of surgical measures to a group of patients heretofore abandoned to their fate.

## PAROXYSMAL HYPERTENSION CAUSED BY PHEOCHROMOCYTOMA OF THE ADRENAL GLAND. ADRENALECTOMY<sup>1</sup>

WILLIAM H. MENCHER, M.D.

The following case is presented because it represents a type of hypertension which is remediable by surgery. The basis for the paroxysmal type of hypertension is a pheochromocytoma or a hormonal producing tumor of chromaffin nature and arising from the medullary portion of the adrenal gland.

The symptom complex produced by these tumors depends on the discharge of large amounts of adrenalin-like or pressor substance into the general circulation and is well illustrated in the case reported below. The diagnosis of this type of tumor is based on one or more of the following: 1) The typical symptomatology in spontaneous or induced attacks; 2) various tests producing a pressor response; 3) the detection in the blood at the height of an attack, by perfusion tests, of pressor substance; 4) the diagnosis and localization of the tumor by perirenal insufflation of gas.

Following the removal of the tumor no further attacks occur and pressor response no longer occurs.

### CASE REPORT

*History.* The patient was a 23 year old Puerto Rican girl. Two and one-half years before admission to this hospital, she began to have episodes of severe frontal and occipital headaches, accompanied by dizziness, weakness, epigastric, back and neck pain, and non-projectile vomiting. Six months later the attacks became more frequent and were associated with choking sensations, dyspnea, orthopnea, palpitation, blanching of the extremities and face, and sweating. During one such attack she was taken to a hospital where she was thought to have a paroxysmal tachycardia. Thereafter attacks occurred at about monthly intervals, most frequently at the end of menses. These attacks were always similar, lasted from fifteen minutes to a few hours, and were followed by a day of weakness, dizziness, and mild headache. A year and a half before admission to The Mount Sinai Hospital she had a very severe attack, associated with marked dyspnea and orthopnea, and she apparently collapsed. She was treated for shock, received oxygen, and was better the next day. Though observed in a hospital for several weeks, again no definite diagnosis was reached. Eleven months before admission here she was readmitted to another hospital during a severe attack, and was observed for five months, during which period a number of typical attacks occurred. Because her blood pressure rose to high levels during the attacks a pheochromocytoma was suspected. During the first attempt to explore the left adrenal region, the induction of anesthesia precipitated a severe attack and a phlebotomy was performed, apparently because of signs of pulmonary edema. Shortly thereafter, the left adrenal was successfully explored but no tumor was found and normal adrenal tissue was removed on biopsy. Postoperatively she continued to have frequent mild attacks as before, although she remained free of serious attacks for about seven months. Ten days before admission a number of severe attacks occurred in rapid succession and she was referred to this Hospital by her physician.

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<sup>1</sup> From the Urologic Service of Dr. A. Hyman. Presented May 26, 1942 at The Mount Sinai Hospital as part of a Symposium on Surgical Aspects of Cardiovascular Lesions, under the auspices of the Thoracic Group.

*Examination.* The patient was a frail but fairly well nourished girl with moderate pallor. The pupils were round, regular, and equal. The fundi showed slight narrowing of the arteries and somewhat hyperemic discs with indistinct margins. The heart was not enlarged or overactive and the second aortic sound equaled the second pulmonic sound. The peripheral arteries appeared slightly thickened. The blood pressure was 140 systolic and 100 diastolic in both arms and 170 systolic and 110 diastolic in the legs. The abdomen was soft and no masses were palpable. The left biceps reflex was more active than the right; the right ankle jerk and knee jerk were greater than the left.

*Laboratory data.* Blood: hemoglobin, 83 per cent; red blood cells, 4,200,000; white blood cells, 7,000 with 64 per cent segmented polymorphonuclear leucocytes, 1 per cent non-segmented forms, 27 per cent lymphocytes, 6 per cent monocytes, 1 per cent eosinophiles, 1 per cent basophiles; platelets, 270,000. Wassermann reaction, negative. Blood sugar, 90 mg. per cent; urea nitrogen, 14 mg. per cent; cholesterol, 230 mg. per cent; icteric index, 3; uric acid 8.1 mg. per cent. Urine: Specific gravity, 1.036; faint trace of albumin; 8-10 white blood cells to the low power field; an occasional red blood cell. An electrocardiogram on admission showed a sinus tachycardia, high QRS,  $RT_{1, 2}$ , and  $3$ , depressed and  $T_1$  inverted. X-ray examination of the abdomen showed the right kidney to be normal in position and size; the left kidney was not clearly delineated. X-ray examination of the chest showed no abnormality of the lungs. Intravenous pyelography showed the right kidney to be relatively small; the pelvis and calyces were within limits; the left upper urinary tract was incompletely outlined but appeared normal.

*Course.* During her stay in the hospital, the patient had frequent attacks, most of which were spontaneous and a few induced. The attacks varied in severity from an hour or more, to the most severe ones lasting 36 hours. Between attacks the patient's blood pressure was usually moderately elevated, ranging from 140 to 160 systolic, and 90 to 110 diastolic. On a few occasions, however, the pressure was entirely normal. A typical attack was characterized by the sudden onset of palpitations, pounding headache, blanching of the face and extremities, abdominal cramps, nausea and repeated vomiting, and eventually marked diaphoresis. Blood pressure readings taken shortly after the onset of these symptoms invariably showed extreme elevation, frequently over 310 systolic (the upper limit of the manometer) and 180 diastolic. When the attack continued beyond 8 to 12 hours, during which period the patient continued to complain bitterly of pounding headache, palpitation, abdominal pain and vomiting, a remarkable chain of events ensued. The major peripheral arteries then showed progressive constriction, the pulse becoming of very small amplitude, until it was entirely obliterated, both by palpation and oscillometric determination. The extremities, including the nose and ears, became extremely pale, cold, and cyanotic. The temperature of the skin determined by means of the Dermotherm, fell as much as  $7.6^{\circ}\text{C}$ . Profuse diaphoresis over the trunk and face was always present at this time and there was usually marked tachycardia, reaching 130 per minute. The neck veins sometimes appeared distended, and the patient often complained of dyspnea. The venous pressure in the antecubital vein, however, was found to be normal during the early part of one attack, and during a later stage collapse and constriction of the veins of the extremities were so great that venipuncture became impossible.

During the height of an attack, with a blood pressure of 270 systolic and 150 diastolic, the fundal arteries were somewhat thinner than normal with a bright irregular reflex and were quite irregular in caliber. They indented the veins slightly and there was a general slight propulsive pulsation. The veins were also irregular in caliber, and were somewhat dilated. Urinalyses during an attack regularly showed an increase in albumin to 3 plus, and the appearance of red blood cells, white blood cells and casts. Slight glycosuria was noted once. The blood sugar was not found to be elevated on the one occasion it was possible to do a venipuncture. Electrocardiograms during an attack showed a sinus tachycardia, high QRS, depressed  $RT_{1, 2}$ , and  $3$  segments, and inverted  $T_1$ . Eventually, after 24 to 36 hours, the patient showed evidence of peripheral vascular collapse, with blood pressure readings obtained as low as 76 systolic and 60 diastolic hemoconcentration, as demonstrated by a hematocrit 53 per cent, tachycardia and torpor, while the evidences of

diminished blood flow through the extremities persisted. The state of shock would last several hours and then gradually the peripheral pulses would become fuller and slow, the extremities warm, the blood pressure would rise to normal levels and the systemic temperature would fall until the whole cycle was repeated with the next severe paroxysm.

*Induction of the attacks.* The usual stimuli for sympathetic discharge were found to produce attacks readily. In analyzing the precipitating factors in the spontaneous attacks, it was found that they had occurred during fear, anger, excitement, sexual intercourse, before meals when blood sugar undoubtedly was falling, and during the induction of anesthesia, when asphyxia was probably a factor.

Similarly, induced attacks were brought on by analogous procedures. A change from the prone to the sitting posture resulted in a rise of blood pressure from 150 systolic and 110 diastolic to 175 systolic and 125 diastolic. Standing then led to a prompt fall in pressure to 155 systolic and 110 diastolic, and then a rapid rise, reaching a peak of 305 systolic and 170 diastolic; in 15 minutes, with a pulse of 80 per minute. Massage of the carotid sinus during this maximum rise caused a prompt fall in blood pressure to 160 systolic and 115 diastolic which, however, immediately rose on discontinuing the stimulation, demonstrating the reflex pathways to be intact and at least potentially active. On reclining, the blood pressure returned to normal only after several hours. Hyperventilation for 3 minutes caused a rise in blood pressure from 170 systolic and 110 diastolic to 305 systolic and 160 diastolic, the pressure not returning to its initial value at the end of one hour. In this instance mechanical massage of the tumor may also have played a role, since at operation the tumor was found to be adherent to the diaphragm. Cold and pain, produced by immersion of the hand in ice water for 2 minutes, caused a rise in pressure from 135 systolic and 98 diastolic to 200 systolic and 135 diastolic within 3 minutes, and this pressure was maintained for over one hour. Attempts to produce paroxysms by massaging the abdomen were uniformly unsuccessful. Studies with insulin, adrenalin, histamine, and other drugs were not carried out because of the severity of the paroxysms. A sugar tolerance test had to be omitted for the same reason.

Differential blood pressures between the brachial artery and the digital arteries during an attack, showed a difference of between 100 and 120 mm. of mercury as compared with 50 mm. of mercury after removal of the tumor, which is within normal limit. This high differential is characteristic of the hypertension produced by adrenalin.

All measures employed to terminate attacks were without avail. Ergotamine tartrate which is an antagonist to adrenalin was completely ineffectual in doses of 1 mg. intravenously. Sodium amytal and other rapidly acting barbiturates gave only slight symptomatic relief, but did not appear to shorten the attacks or to lower the blood pressure except transiently.

*Roentgenologic demonstration of the tumor.* Perirenal insufflation was performed. Instillation of 550 cc. of oxygen into the right perirenal space was carried out without any untoward reaction. X-ray examination revealed a suspicious mass in the right adrenal area, the lower portion of which was flattened and caused flattening of the upper pole of the kidney.

*Pre-operative preparation.* Because of the dangers of emotional excitement, preparations were made to "steal" the adrenal. Avertin was given as a basal anesthetic. The patient was given desoxycorticosterone acetate intramuscularly and saline intravenously pre-operatively, adrenal cortical extract intravenously during the operation, and adrenalin and adrenalin-in-oil during and after the operations.

*Operation.* Adrenalectomy for pheochromocytoma of the right adrenal gland was performed under cyclopropane anesthesia.

Through a five inch right lumbar incision the renal area was exposed, the kidney was mobilized and retracted downwards. The adrenal area was found to be the seat of a tumor the size of a large plum. The twelfth rib was then excised in order to afford more adequate exposure of the adrenal area. A tiny perforation in the pleura was immediately closed by sutures.

The tumor was round, semi-soft and was attached to the upper pole of the kidney. The

kidney and tumor were separated easily from each other and the tumor was thus well outlined and mobilized. The inferior vena cava was easily seen as well as the blood supply of the adrenal. This supply consisted of the adrenal vein from the renal vein, another adrenal vein directly from the inferior vena cava, and smaller twigs coming directly from the diaphragm to which the tumor was somewhat adherent.

At the onset of operation the blood pressure was 120 systolic. As soon as the tumor was palpated, the blood pressure rose to 220 systolic at which level it was maintained almost constantly until the last vessel running to the adrenal gland was tied. Within a few minutes after tying off of the last vessel, the blood pressure dropped precipitously to 110 and then further down to 70 systolic. The tumor was easily removed. The kidney was replaced into position after placement of two iodoform packings to the adrenal area. The wound was closed with interrupted figure-of-eight chromic sutures.

*Postoperative course.* During the first twelve hours postoperatively the blood pressure ranged between 70 and 90 systolic and 50 and 65 diastolic, but the patient's general condition was relatively good. Thereafter, the blood pressure was maintained at about 100 systolic and 60 diastolic, and her course was uneventful. The patient became entirely free of spontaneous and induced attacks.

On examination three months after the operation, she had gained twenty pounds in weight. Subsequently the patient became pregnant. Her period of gravidity was uneventful.

*Pathology.* The specimen consisted of a greatly enlarged adrenal gland weighing 31 Gm. On section, "the enlargement of the gland is seen to be due to the presence of a tumor which occupies the central portion of the gland and uniformly expands it. The golden yellow cortex is distinctly visible over the surface of the tumor as a narrow zone varying in thickness from less than a millimeter to 3 mm. in thickness. Microscopically, the tumor had the characteristic structure of a pheochromocytoma.

*Bioassay.* Bioassay of the tumor showed each gram of tumor caused a reaction in the denervated cat's iris, equivalent to that caused by 8 mg. of adrenalin.

# ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

## CHAPTER 2

### THE BIOLOGY OF HYPERTENSION OF THE GREATER CIRCULATION

In a recent publication (1) the following currently recognized causes of hypertension of the greater circulation were discussed: 1) psychological; 2) sequelae of persistent Graves' syndrome; 3) renal disease; 4) adrenal blastomata or paragangliomata; 5) congenital peripheral resistances; 6) increased intracranial pressure; 7) carotid sinus dysfunctions; 8) lead poisoning; 9) Cushing syndrome. Of these all but the first two represent processes in which morbid anatomy comes first and hypertension follows. In the hypertension of psychologic origin or in that following persistent Graves' syndrome, the hypertension is primary in the sense that it is the first clinical manifestation and for this reason the term essential hypertension has been applied.

Elsewhere (2) I have discussed more fully the attributes of patients with essential hypertension. Psychically, they represent the antithesis of the child in mental make-up. They do not play and they do not exercise. They live compact, crowded lives with none or few avocations; they are insecure, mentally inelastic, look far forward into the future and so construct their life plan. Their mental horizon is narrow but within this range they pursue their aims with a grim determination. Physically, individuals with hypertension tend to be short, small necked, stocky individuals, unathletic in type and usually overweight but not necessarily obese. Statistics are eloquent (3) that weight is a conditioning influence upon the development of hypertension, especially with advancing years. Testimony is strong that there is a familial tendency to develop hypertension (O'Hare, Walker and Vickers (4), Weitz (5)) but how far this is the result of genotypic or environmental influences it is difficult to say. There has been a definite increase in incidence of hypertension in the last few decades, if one may judge by the present appalling increase in mortality from the cardiovascular-renal syndrome. I believe this increase is the result of the increasing stresses and strains, economic and social, that modern civilization entails. As evidence, we cite the striking increase in hypertensive disease in the northern Negro, whereas in the heart of Africa hypertension is almost unknown (Donnison (6)).

In other words, essential hypertension, like an infection, is the result of a

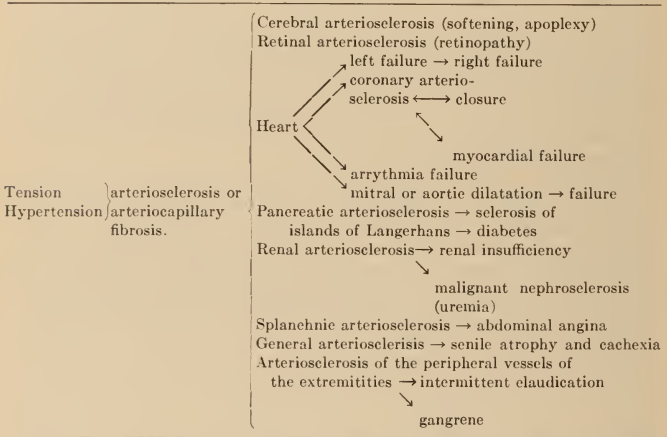
<sup>1</sup> This is the second in a series of essays by Dr. Eli Moschcowitz in which an attempt is made to interpret certain forms of chronic disease from the biologic viewpoint as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans these essays will appear in consecutive issues of the *JOURNAL OF THE MOUNT SINAI HOSPITAL*. It is also quite probable that when the publication of the projected series of essays is completed, the several installments will be assembled and printed in a monograph, should the demand for such a volume justify the step.—Ed.

background and an insult. There has been a strong trend in recent years to view essential hypertension as a psychosomatic disease.

The biologic evolution of essential hypertension is manifold. Clinically it is manifested by one or more evidences of the cardiovascular-renal syndrome which is a compound of a host of anatomical and functional characters. The latter are partly the result of the anatomical changes and partly due to the stresses and strains that the hypertension imposes upon the cardiovascular system.

TABLE



This table illustrates why the different evolutions of hypertension and arteriosclerosis are seldom biologically pure. Combinations of these manifestations are the rule rather than the exception.

Why one or the other organs should be predominantly involved in such a generalized process is an intriguing problem. The concept of *Organminderwertung* only begs the question. Nor has the problem of the different tempo ranging, in musical terms, from *adagio* to *presto* that hypertension undergoes, been satisfactorily explained.

The primary anatomical event is arteriosclerosis which at first is strictly limited to the vessels of the greater circulation. The proof that arteriosclerosis follows hypertension and does not precede it, lies, as I have pointed out in Chapter I, in the independence in incidence between arteriosclerosis of the greater and pulmonary circulation. Unfortunately, in the past the study of arteriosclerosis has been largely confined to the vessels of the greater circulation but if simultaneous observations are made upon the vessels of both circulations, it will be discovered that as a rule arteriosclerosis is present only in the greater circulation and not in the pulmonary and vice versa, and when both are present simultaneously it is the exception rather than the rule. Arteriosclerosis of the pul-

monary circulation is practically confined to the conditions I have outlined in Chapter I, namely, to mechanisms that produce an increased pressure in the pulmonary circuit, such as mitral disease, emphysema, a failing heart, etc. The argument has been frequently advanced that arteriosclerosis cannot be due to hypertension because it is so frequently present with normal pressures, the so-called "senile" or "decreased" arteriosclerosis of Allbutt. These observers fail to consider that hypertension is not an absolute but a relative value and represents an exaggeration of the normal intravascular tension.

The reason why the pulmonary artery is comparatively free from arteriosclerosis is because the normal pressure in the pulmonary artery is only one-sixth that of the aorta (Starling (7)). Even when the pressure in the pulmonary artery is raised to its highest value, it probably never approaches the systemic pressure, so that if such pressures can produce gross arteriosclerosis of the pulmonary artery, there is every reason for assuming that the normal systemic pressure, given sufficient time, can produce arteriosclerosis of the greater circulation. In other words, arteriosclerosis in the anatomical sense is a normal involutionary process. Hypertension brings it sooner (accounting for practically all cases of juvenile arteriosclerosis) and intensifies the process.

These remarks apply only to what may be termed gross arteriosclerosis, that is, lesions that are visible to the naked eye, which are present in every human being after the twentieth year. (Mönckeberg (8)). Microscopically, arteriosclerosis may be said to begin at birth, a process that may be termed "physiological ageing." At birth, the intima of the elastic arteries is exceedingly thin, consisting only of an endothelial layer lying almost directly upon delicate elastic lamina. With age, the intima thickens from 6 microns at birth to 190 at the age of 70 (Schäfer (9)). Splitting of the elastica occurs as early as the second year (Hallenberger (10)) and progressively increases with age. The media also thickens with the growth of the body from 650 microns at birth to 1111 at the age of 70 (Schäfer (9)). These changes have been noted in most of the vessels of the body (for references see Moschcowitz (1)). Now the essential lesions of arteriosclerosis are thickening of the intima, splitting of the elastica and hypertrophy of the muscular coat, the last especially prominent in the presence of hypertension. (Atheroma, in my opinion, is only a facultative lesion in arteriosclerosis, as shown by its practical absence in arteriolosclerosis). These hyperplastic processes may therefore be regarded as the juvenile expressions of the matured lesions and represent compensatory mechanisms for the progressive increase in intravascular pressure that proceeds from birth to old age (Aschoff (11)). As evidence we cite the intensification of these processes in the presence of hypertension. The term "hyperplastic" arteriosclerosis (Evans (12)) is aptly applied. In other words, physiological ageing and functional adaptation merge imperceptibly into anatomical, but not necessarily into clinical disease.

Identical processes are at work in the genesis of phlebosclerosis. In every instance of true phlebosclerosis, a condition that causes an increased pressure within the vein may be predicated (13).

Furthermore, analogous processes and mechanisms are in evidence in the

capillaries of certain organs. Sclerosis of the capillaries has been especially studied in the lung, the kidney, the pancreas and in the liver. In the lung, especially, the biology of the lesion can be easily studied (13) in hypertension of the pulmonary circulation, from a simple dilatation with fibrosis and perhaps hyalinization of the walls of the alveoli in the earliest stages to extensive fibrosis and obliteration of the walls and perhaps reversion to the embryonal type of lung in the advanced phases. These capillary lesions are always accompanied by gross arteriosclerosis of the pulmonary vessels. In the pancreas, fibrosis and hyalinization of the capillaries of the islands of Langerhans are practically always associated with gross arteriosclerosis of the larger vessels. In the kidney, sclerosis and hyalinization of the capillaries identical in morphology to those in the lung and pancreas are exceedingly common especially in association with hypertension (14), and again is accompanied by gross arteriosclerosis of the renal vessels. In the liver, the capillaries around the central veins show sclerosis and is progressive not only with the duration of the malady, but also with the intensity of the hypertension of the pulmonary circuit as gauged by clinical standards. It is most pronounced, for instance, in tricuspid disease, when the pressure in the right heart must be unusually high. The intensification and spread of the capillary sclerosis is responsible, to my view, for the genesis of cardiac cirrhosis (15). This hepatic capillary sclerosis only occurs with hypertension of the pulmonary circuit, and the mechanism of its development is due to the transmission backward of the pressure into the vena cava, thence to the hepatic veins and finally to the capillaries around the central veins. Whenever this capillary sclerosis is marked, especially in the stage of cardiac cirrhosis, the hepatic veins show a marked phlebosclerosis.

In summation, the lesions in these organs represent a true arteriocapillary (or as in the liver, a venocapillary) fibrosis. The capillary lesions are in a large measure responsible for some of the clinical phenomena. In the lung, they undoubtedly contribute to the anoxemia due to the difficulty in the exchange of oxygen through the thickened capillary wall. In addition, by the narrowing and sometimes obliteration of the alveoli they reduce the vital capacity. In the pancreas, the lesions cause diabetes, in all likelihood by the diminished production of insulin. In the kidney, the lesions in the glomeruli contribute many of the phenomena of renal insufficiency; lowering of concentration, proteinuria and eventually azotemia. In the liver, the venocapillary fibrosis causes various degrees of hepatic insufficiency.

Whether the concept of arteriocapillary fibrosis can be applied to other viscera such as the brain, retina, heart, spleen and organs of internal secretion is a matter for future study but judging by analogy, the probability is strong that it does. The difficulty lies in the morphologic study of single capillaries. In the organs cited above the task is comparatively simple because the capillaries occur in isolated groups. At all events, clinicians are aware that all these organs supplied by the greater circulation in addition to those mentioned above are sometimes affected by disease, either singly or simultaneously, and they accomplish such results by either reducing the blood supply by thrombosis consequent

to disease of the lining and resulting occasionally in embolism, or by rupture of an affected vessel.

*A. Brain and cerebrospinal system.* The clinical phenomena are characterized by such symptoms as apathy, dullness, loss of memory, headache, dizziness, occasionally delirium, hallucinations and at times, the involutional psychosis of senility. If death comes as the direct result of cerebral arteriosclerosis, it usually comes through cerebral hemorrhage or thrombosis.

There is another complication in the cerebrospinal system that frequently follows hypertension of the greater circulation, namely hypertension of the cerebrospinal fluid as determined by the spinal tap. Clinically it is manifested by severe headache, occasional nuchal rigidity, increased peripheral reflexes, occasional slight exophthalmos, and usually papilledema. A few years ago, Kessler, Moschowitz and Savitzky (16) studied the mechanism whereby this syndrome arose in hypertension and concluded that it was largely the result of an increase in the permeability of the cerebrospinal barrier as determined by the Walther-Hauptman test, and in occasional instances, a superimposed increase in venous pressure due to complicating cardiac failure. It rarely occurs except in so-called "malignant hypertension" or "malignant nephrosclerosis".

*B. Retina.* The changes in the retina in hypertension vary from a mild form in which increasing tortuosity of the arteries with compression of the veins is the only manifestation to the advanced form of retinopathy in which narrowing or even obliteration of the arteries, exudates, hemorrhages and papilledema are the features. It is generally agreed that the lesions of hypertensive retinopathy represent an arteriosclerosis of the retinal and choroidal vessels (Collins and Mayou (17)) and in my experience the graver forms of retinopathy, i.e., with exudates and hemorrhages, rarely occur unless a diastolic pressure of 120 mm. Hg has been maintained over a prolonged period. The systolic pressure seems to bear little or no relation to the retinopathy. Once a retinopathy has developed of the graver variety with hemorrhages and exudates, it is persistent and one can predict that death is not far off. The only exceptions are conditions in which a marked drop in diastolic pressure has resulted. I have witnessed disappearance of a retinopathy in acute glomerulonephritis, in eclampsia after delivery, and after bilateral sympathectomy for hypertension.

*C. Heart.* Cardiac involvement is responsible for the majority of deaths. There are a number of eventualities which may bring this about.

1. Left sided cardiac failure. When the primary compensatory adjustments of hypertrophy and dilatation eventually breaks down, the heart is no longer able to pump sufficient blood to provide for the continuous inflow from the right heart; the blood stagnates in the lungs and the classical picture of left sided failure ensues with oliguria, nocturnal dyspnea and orthopnea. The venous pressure is usually low.

2. Right sided failure. When attacks of left sided failure have continued for a period of months or years, a compensatory mechanism may again restore comparative well being by causing a hypertension of the pulmonary circuit with dilatation of the pulmonary arterial tree. In turn the right heart hypertrophies

and dilates but eventually the muscle breaks down under the continuous strain and the clinical picture of right sided failure ensues, with anoxemia, exertional dyspnea, cyanosis, increased venous pressure, prolonged circulation time, enlargement of the pulmonary conus, swelling of the liver, anasarca (see Chapter I). The nocturnal attacks of dyspnea and the orthopnea are now relieved but from now on the history is one of repeated attacks of failure with chronic invalidism. Hypertension thus brings into being a whole series of compensating mechanisms which, if the patient lives long enough, follow each other in orderly sequence, with intervals of failure. In both these types of failure, the mechanisms may be interpreted in terms of disordered function rather than of morbid anatomy. Bell and Clawson (18) report that in their series, 44 per cent of their cases died from myocardial insufficiency.

3. Coronary disease. In Bell and Clawson's series, 16 per cent died of coronary disease. Unless the patient dies in an attack of closure, coronary disease results in left sided failure and eventually right failure exactly as in 1 and 2.

4. Dilatation of mitral and aortic rings. Either aortic or mitral insufficiency may result, partly due to the dilatation of the left ventricle or of the aortic ring, and partly to sclerosis of the valve consequent to the increased pressure.

5. Arrhythmias. Almost every variety of abnormal cardiac rhythm may follow hypertension with or without coronary disease; extra-systoles, auricular fibrillation, partial or complete heart block, nodal rhythm. These indirectly contribute to the production of cardiac failure. Ventricular fibrillation frequently ushers in sudden death.

*D. Pancreas.* Hypertension of the greater circulation and diabetes are common associations. Joslin (19) finds that 19 per cent of diabetics between 21 and 50 years of age, and 33 per cent of those over 50 have hypertension. Kramer's (20) figures inclusive of all ages is 39 per cent. That sclerosis and fibrosis of the islands of Langerhans and sclerosis of the vessels of the pancreas are usually associated is admitted (Opie (21), Cecil (22), Warren (23)) and the presumption is strong that they are the direct cause of adult diabetes by lessening the production of insulin. Diabetes cannot be the cause of arteriosclerosis because in cases uncomplicated by hypertension of the pulmonary circulation, the pulmonary vessels are perfectly free. As Joslin (19) points out, the most common causes of death in patients with diabetes, since the discovery of insulin, are arteriosclerotic manifestations.

*E. Kidney.* Some degree of nephrosclerosis nearly always follows essential hypertension varying from a minimal involvement in which only scattered glomeruli are involved to such an extensive sclerosis that only traces of normal renal architecture are preserved. Grossly, a host of kidneys may be placed in series, varying in size from normal to a kidney that weighs only a few grams. The latter may be fittingly termed an end result, and has passed through the intervening stages. It is generally agreed that the contracted phase is the result of progressive narrowing or occlusion of the terminal arteriosclerotic vessels (MacCallum (24)). It is not clear why the vessels of the kidney show more widespread arteriosclerosis than in the rest of the general vascular system

(Bell (14)). Probably all individuals with essential hypertension would develop contracted kidneys provided they lived long enough. Unfortunately about nine-tenths die either of a cardiac complication or an irrelevant disease, comparatively early in the life cycle of the disease, even in the initial phase (25). Only about one-tenth therefore die of renal insufficiency.

Clinically, these progressive morphologic changes are paralleled by varying degrees of renal insufficiency. The first effect is a loss in concentrating power thus interfering with the excretion of harmful substances (urea, electrolytes, phosphates, etc.). The organism compensates by an oliguria and so a progressive lowering of the specific gravity of the urine occurs until it attains a value of 1010 isotonic with the glomerular filtrate which is deproteinized plasma. This phase is called by Fishberg (26) the compensated phase of renal insufficiency. After this, the kidney can no longer pass sufficient urine to maintain the normal quota in the blood so that these substances accumulate causing disturbances in the acid base equilibrium and uremia. This represents the decompensated phase of renal insufficiency. Proteinuria sooner or later appears; it rarely is sufficient to give a hypoproteinemia with its consequences. Partly as the result of the phosphatemia and partly from the loss of calcium by way of the proteinuria (if of sufficient degree) a hypocalcemia results, to compensate for which, the parathyroid glands enlarge (Pappenheimer and Wilens (27)). The renal insufficiency may be aggravated by an associated cardiac failure.

The term "malignant hypertension or malignant nephrosclerosis" has been applied to that clinical expression of the disease where the terminal event is complete or nearly complete renal failure with "uremia". Nosologically some have conferred upon this expression the distinction of a separate entity because it usually occurs in younger subjects, has a more rapid tempo and morphologically is nearly always accompanied by necrosis of arterioles, especially in the efferent vessels of the glomeruli. That it is not a separate disease is shown by the following observations: 1) The rapid tempo is only apparent. The hypertension antedates the history as given by the patients by many years, as I have observed only too frequently. The patient dates the beginning of his disease from the time he was clinically incapacitated. 2) It occurs in older subjects not uncommonly. 3) The necrotic lesions occur not only in essential hypertension but with glomerulonephritis. In my observations, these lesions are nearly always accompanied by prolonged high diastolic pressures. This is in accord with the observations of Goldblatt (28) who obtained such lesions in experimental hypertension.

*F. Extremities.* Clinically, arteriosclerosis of the lower extremities in essential hypertension is manifested by a whole range of symptoms and signs varying from intermittent claudication to gangrene, depending on the degree of narrowing. The narrowing is often aggravated by the association of Mönckeberg's sclerosis which is exceedingly common in the lower extremities. Why the upper extremities are comparatively immune from the ravages of arteriosclerosis is problematic. "Diabetic" gangrene is strictly speaking an arteriosclerotic gangrene complicated by diabetes.

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## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Ureteral Obstruction Due to Calculus Following Total Hysterectomy.* G. D. OPPENHEIMER AND S. WIMPFHEIMER, J. Urol. 47: 444, April 1942.

This case was reported because of the unusual clinical picture presented. A 50 year old woman without previous urologic complaints developed symptoms and signs of a unilateral blockade of the lower end of the ureter following a total hysterectomy. Ordinarily this would have suggested accidental occlusion of the ureter by a ligature. Diagnostic study however revealed an obstructing ureteral calculus. Operative removal of the concretion was performed.

*The Use of Concentrated and Purified Antitoxic B. coli Serum in the Treatment of Indeterminate Ulcerative Colitis.* A. WINKELSTEIN AND G. SHWARTZMAN. Am. J. Dig. Dis. 9: 133, April 1942.

The authors conclude that indeterminate ulcerative colitis is a disease in which B. coli may play an important pathogenic role as a secondary invader.

Whole and concentrated horse serum strongly antitoxic to B. coli has been prepared according to the principles of the Schwartzman Phenomenon.

The present communication deals with 29 new cases treated with concentrated antitoxic B. coli horse serum which supplements a previous report dealing with 41 cases in a high percentage of which beneficial effects were obtained by means of the antitoxic whole horse serum.

Of the 29 cases described in this paper, 20 were greatly benefited; in two cases the results were questionable and the remaining 7 failed to show improvement.

In view of the encouraging results, the intramuscular use of concentrated antitoxic B. coli horse serum (Schwartzman) is advocated for treatment of severe and intractable cases of indeterminate ulcerative colitis.

*Biologic Assay of the Estrogens in Pregnancy Blood.* M. A. GOLDBERGER AND R. T. FRANK. Am. J. Obst. & Gynec. 43: 865, May 1942.

Ether and alcohol extracts (combined) of 86 bloods covering the fifth to fortieth weeks of pregnancy were assayed on castrated mice. The estrogens increased progressively to term. Not until the seventeenth week was reached did the level exceed the maximum of estrogens found in the blood of non-pregnant women. In the fifth week, the amount approximates 25 mouse units per liter (MU/L), at term 1000 MU/L.

Hydrolysis of the blood does not increase the yield; hence the estrogens probably circulate as free estrogens. Some parallelism appears to exist between the increase of blood estrogens and the increase of free urinary estrogens in pregnancy.

*The Respiration in Myasthenia Gravis.* D. LASZLO AND F. C. REDLICH. Am. J. Med. Sc. 203: 693, May 1942.

The authors studied certain aspects of the respiratory function in patients with myasthenia gravis such as (1) vital capacity, its changes in relapses and during remissions as

induced by prostigmine. (2) The muscular and diaphragmatic movements as determined by roentgenographic methods. (3) The degree of oxygenation of the arterial blood. They found the vital capacity greatly reduced due to inefficiency of the diaphragm and auxiliary muscles concerned in breathing. Changes in vital capacity parallel closely alterations in the general state. The therapeutic effect of prostigmine could be easily gauged on the increase in vital capacity and on roentgenographic evidence of increased diaphragmatic movements. In spite of extremely impaired respiratory function in myasthenia gravis, no apparent interference with the oxygenation of the blood in the lungs was found.

*Death During Sulfathiazole Therapy. Pathologic and Clinical Observations on Four Cases with Autopsies.* M. LEDERER AND P. ROSENBLATT. J.A.M.A. 119: 8, May 1942.

Four autopsied cases are described in which death attributable to sulfathiazole was associated with focal necrotic lesions which were widely disseminated throughout the viscera. Cultural and histologic search failed to demonstrate bacteria in the lesions. The decision whether they were the result of direct toxic action of sulfathiazole or due to acquired sensitivity to prolonged ingestion of the drug could not be made. Clinically, in each case sulfathiazole was given uninterruptedly. During therapy, a sudden episode of chills and fever, sometimes associated with a rash, conjunctival injection, myalgia, and arthralgia occurred. These symptoms were interpreted as infective in origin and the drug was continued in the original or in increased amounts. However, the fever persisted, coma developed, and in 2 cases, anuria became a prominent feature.

*Duplicate Measurements of Circulation Time Made with the Alpha Lobeline Method.* A. LILJENFELD AND K. BERLINER. Arch. Int. Med. 69: 739 May 1942.

The lobeline test is an objective method of measuring the velocity of blood flow. Alpha lobeline hydrochloride stimulates the respiratory center by way of a reflex from the carotid sinus; the result is a cough which serves as the end-point of the test. When this test was used to evaluate the progress of patients suffering from heart failure, the day to day variations observed in the same patient were found considerable. To determine whether factors other than changes in the degree of heart failure might be operative, one hundred duplicate measurements of circulation time with an interval varying from 15 to 60 minutes were made.

Marked differences in the results of the duplicate tests were the rule rather than the exception; these differences varied from 3 to 199 per cent in 85 cases, with an average variation of 29 per cent. The result of the second test was higher than that of the first just as frequently as it was lower. In only three cases were identical results obtained. In twelve cases the second injection failed altogether to produce cough.

Differences in the results of duplicate tests were greatest in patients suffering from congestive heart failure.

Circulation time tests in general and the alpha lobeline test in particular should not be relied on to evaluate the progress of a patient with congestive heart failure unless the changes shown by these tests are marked.

*Treatment of Asthmatic Paroxysm with Nicotinic Acid.* F. E. MAISEL AND E. SOMKIN. J. Allergy 13: 397, May 1942.

The marked vasodilator properties of nicotinic acid suggested its use in the treatment of bronchial asthma. Severe asthmatic paroxysms were controlled in sixteen of twenty-one patients by the intravenous injection of 0.1 grams of nicotinic acid. Relief was obtained from within three to fifteen minutes following the injection and seemed to coincide with the development of the flush. The period of benefit from a single injection often lasted from one to two days in patients who were taking one to four injections of epinephrine a day. Oral medication in doses of 0.2 grams before meals also seemed efficacious in five of nine chronic asthmatic patients. The drug is quite non-toxic aside from the minor unpleasantness of the flush and occasional mild epigastric sensations. Tolerance did not seem to develop during the period of observation.

*Tuberculosis of the Breast Treated with Roentgen Irradiation.* S. RICHMAN. Am. J. Roentgenol. 47: 771, May 1942.

Tuberculosis of the breast occurs infrequently and then usually in women between the ages of twenty to forty. The differential diagnosis from cancer of the breast may be impossible when ulceration and sinus formation have not yet occurred. Biopsy of the abscess wall is advisable in cases of breast abscesses which do not heal promptly under conventional therapy. Since local excision of the involved segment of the breast is reported to be unsuccessful in many cases, simple mastectomy must be done for cure. Roentgen therapy is recommended in tuberculosis of the breast as a conservative and successful form of treatment. A case of tuberculosis of the breast is presented which was treated with roentgen irradiation and is now free of disease twenty-nine months after the last treatment.

*An Improved Method of Obtaining Sustained Controlled Hyperpyrexia with Triple Typhoid Vaccine.* H. A. SOLOMON AND E. SOMKIN. Am. J. Med. Sc. 203: 736, May 1942.

A method for obtaining controlled sustained hyperpyrexia with a continuous infusion of triple typhoid vaccine in saline is described. The technique consists essentially of adding small amounts of triple typhoid vaccine to saline in the amounts one would ordinarily use for a single injection of the vaccine. Once the chill has occurred there is a moderately controllable relationship between the rate of delivery of the organisms in the infusion and the height and duration of the febrile response. Its advantages over the single injection technique is that it is safer, controllable and that a more sustained and elevated temperature is obtainable. Using this method in sixteen cases for a total of sixty-seven treatments the temperature was maintained over 104°F. for an average of four hours and twenty minutes. It is believed that the combined use of the sulfonamides and hyperpyrexia by this means offer a therapeutic agent which is far more potent than that of the sulfonamides alone.

*Sulfanilamide for Treatment of Gonorrhea of Anal Canal.* R. TURELL. J. Lab. & Clin. Med. 27: 1046, May 1942.

The author proposed sulfanilamide chemotherapy for anal gonorrhea in the absence of localized suppurations or poorly draining sinuses. The plan of treatment consisted of the oral administration of 1 Gm. of sulfanilamide every four hours for 24 to 30 doses, which resulted in a concentration of from 6 to 11 mg. of free sulfanilamide in each 100 cc. of blood. Thereafter, the drug was reduced to from 3 to 4 Gm. daily and was continued for a period of from four to five weeks. This plan of sulfanilamide therapy was found safe for the patient who is under daily medical supervision.

Sulfanilamide has recently been superseded by sulfathiazole or sulfadiazine.

*Photoelectric Determination of dl- $\alpha$ -tocopherol in Serum.* G. G. MAYER AND H. SOBOTKA. J. Biol. Chem. 143: 695, May 1942.

The amount of dl- $\alpha$ -tocopherol in samples of human serum of 10 ml. or less may be determined in the photoelectric colorimeter by a method consisting of an adaptation of the  $\alpha$ , $\alpha'$ -bipyridine-ferrie chloride method of Emmerie and Engel. A number of details of procedure are pointed out.

*Hypertension Due to Renal Embolism.* A. M. FISHBERG. J.A.M.A. 119: 551, June 1942.

Five cases are described in which unilateral or bilateral renal embolism was followed by pronounced rise in arterial pressure. Three of the patients had mitral stenosis and two had myocardial infarction due to coronary disease. One of the patients survived the embolization and the blood pressure returned to its previous level. The hypertension resulting from renal embolization represents perhaps the most unequivocal illustration as yet observed of the occurrence of the Goldblatt phenomenon in man.

*Treatment of Bacterial Meningitis of Rhinogenic Origin.* R. KRAMER AND M. S. SOM. *Ann. Otol., Rhin. & Laryng.* 51: 499, June 1942.

Nineteen cases of bacterial meningitis of rhinogenic origin were all treated with large doses of sulfonamides plus antisera and transfusions as indicated. Thirteen of these were treated surgically in addition to chemotherapy. Six of this group made complete recoveries by this combination of surgery and chemotherapy and seven died. All of the six patients who were treated by chemotherapy alone died.

Chemotherapy has proved invaluable in sterilizing the meninges after the initial invasion from a focus in a neighboring nasal sinus. Reinfection of the cerebrospinal fluid is to be expected unless the primary focus is adequately drained surgically. The sulfonamides alone have been found ineffective both in controlling the suppuration in the sinuses and in preventing the complications of osteomyelitis and brain abscess. The routine use of these drugs in the treatment of acute sinusitis seems to be inadvisable. The sulfonamides may mask the early clinical symptoms and signs of a serious complication which are apt to become manifest on withdrawal of the drug.

The use of chemotherapy in combination with surgery has yielded cures in cases of bacterial meningitis of rhinogenic origin. The patient in this type of case almost invariably succumbed before the advent of the sulfonamides. Patients who are desperately sick and toxic from an overwhelming infection of the meninges should first be treated with sulfonamides and supportive treatment before operation on the sinuses.

*Neuro-Circulatory Asthenia and Related Problems in Military Medicine.* B. S. OPPENHEIMER. *Bull. New York Acad. Med.*, 18: 367, June 1942.

During the present war the problem of handling registrants and men in the Army and Navy presenting the syndrome called neuro-circulatory asthenia has arisen again. This paper reviews the progress in this subject since 1917, beginning with a discussion of the terminology and why the term neuro-circulatory asthenia was introduced. Neuro-circulatory asthenia appears to be the somatic component of a psychosomatic state. It is important from a military standpoint because it earmarks those men who are potential candidates for an anxiety or some other form of psychoneurosis. The condition is described as "an abnormal reactivity of the nervous system including the innervation of the entire circulatory system." The symptoms are both physiologic and psychologic. A possible mechanism from the psychology point of view is suggested. The psychological aspects, especially conflicts in such individuals as are constitutionally predisposed, are emphasized. The frequency and importance of the family history and the previous personal history in respect to psychoneurotic factors are given statistical consideration. Following this there is a description of the clinical picture, physical signs, differential diagnosis and the prognosis. No specific treatment has been discovered, but there are many suggestions to prevent the onset of this incapacitating condition during war time, to assist in its early recognition, and its treatment when it has become an incapacitating disorder among soldiers. More fundamental research work especially along pharmacologic lines should be done on this condition, and it is pointed out that it would be most appropriate that Americans should pursue these investigations, as the first vivid clinical description of neuro-circulatory asthenia was made in 1871 by a Philadelphia clinician Dr. Jacob M. DaCosta.

*A Detailed Description of the Technique for Androgen Assay by the Chick Comb Method.* R. T. FRANK, E. KLEMPNER, F. HOLLANDER, AND B. KRISS. *Endocrinology*, 31: 63, July 1942.

This article presents for the first time all of the technical details of the authors' chick comb method for androgen assay. It includes 1) preparation of material for assay; 2) conditions and technique of the procedure; and 3) the method of calculating the final result. The latter is presented in such a way that the calculations can be performed either by direct application of the dose-response equation previously reported (involving the weight of comb, initial and final body weights, and the number of chicks of each sex) or by the use of a

chart which employs only simple arithmetical procedures. This chart is presented together with an illustrative example. For uniform comparison of data, it is stressed that all the details of technique be followed without variation.

*Diagnosis and Treatment of Concomitant Squint.* J. LAVAL. Dis. Eye, Ear, Nose & Throat. 2: 202, July 1942.

A differential diagnosis is established between concomitant squint and paralytic squint and the methods for diagnosing these two are explained. Indications for the prescribing of plus or minus lenses in convergent and divergent squint are established and the methods of measuring the amount of squint for distance and for near and in the six cardinal positions are reviewed. The indications for surgery are thoroughly examined and the different methods of operation are explained.

*Unilateral Renal Disease and Renal Vascular Changes in Relation to Hypertension in Man.*

B. FRIEDMAN, L. MOSCHKOWITZ, AND J. MARRUS. J. Urol. 48: 5, July 1942.

We have studied the data in 193 patients in whom nephrectomy was performed for unilateral renal disease.

The mean blood pressure and incidence of hypertension was no greater in this group than in comparable control series of patients.

After removal of the diseased kidney the blood pressure level remained essentially unchanged in the majority of the patients whether hypertensive or normotensive before operation. Twenty-two per cent of the individuals with normal blood pressure before operation developed hypertension postoperatively. A significant decline in blood pressure occurred in only 7 per cent of the subjects who had had hypertension before nephrectomy.

The incidence of hypertension was higher in the patients in whom there was good excretory function than in a comparable group with poor or absent urine excretion in the diseased kidney.

When unilateral renal disease and hypertension co-exist, removal of the diseased kidney is not likely in the majority of cases to result in a reduction of blood pressure. The advisability of nephrectomy in most cases should therefore rest primarily on the nature of the renal disease rather than on the expectation of lowering the blood pressure.

*The Etiologic Role of the Intrarenal Pelvis in Hypertension.* A. HYMAN AND N. C. SCHLOSSMAN. J. Urol. 48: 1-4, July 1942.

In a recent article Ravich postulated the hypothesis that the intrarenal type of pelvis is an important predisposing factor in hypertension. It is suggested these minor obstructive uropathies increase intrarenal pelvic pressure sufficiently to encroach upon the adjacent renal blood vessels. The ensuing partial occlusion of the blood vessels simulates the conditions of the Goldblatt experiment in the production of nephrogenic hypertension. Hyman and Schlossman after studying a series of fifty-five autopsies, reviewing two hundred unselected intravenous urograms and a large series of pyelograms showing various types of pathology associated with intra and extra renal pelvis, also experimental data on animals, came to the conclusion that there was no relationship between hypertension and the type of renal pelvis.

*Report on Assays of Known Quantities of Androsterone by the Chick Method.* E. KLEMPNER, F. HOLLANDER, R. T. FRANK, AND B. KRISS. Endocrinology, 31: 71, July 1942.

In order to demonstrate the reliability of the authors' method for androgen bio-assay (chick comb technique) data are reported for 39 determinations with different amounts of crystalline androsterone. These observed values are compared with the expected and percentage errors indicated. The practicability of the method is shown by a mean error of less than 25 per cent over the entire dosage range, and about half this in a restricted dosage range.

*Acanthosis Nigricans Associated with Carcinoma of the Lung.* O. L. LEVIN AND H. T. BEHRMAN. Arch. Dermat. & Syph. 46: 54, July 1942.

The diagnostic value of cutaneous lesions in the province of internal medicine is aptly illustrated by the dermatosis entitled acanthosis nigricans. This disease is uncommon, but it is so frequently associated with carcinoma of the internal organs that its positive diagnosis may be considered an indication for exploratory laparotomy.

In the adult or malignant form of acanthosis nigricans, the usual concomitant growth is a carcinoma of the stomach. The association of this pigmentary disorder with a malignant growth of the lungs has been reported in only two cases.

A review of the literature reveals the rare occurrence of acanthosis nigricans with pulmonary carcinoma. In the case reported here the occurrence of the lesion on the abdominal skin suggested a possible relation to abdominal carcinoma, especially of the organs involved in pigment formation and deposit. The associated pulmonary symptoms were suggestive of a primary focus in the lungs with secondary metastases to the abdominal organs, which proved to be correct on post-mortem examination. It is emphasized that apparently minor cutaneous changes, such as pigmentation, may be of value in the early diagnosis of visceral carcinoma.

*Common Duct Obstruction Due to Primary Carcinoma of the Cystic Duct. Resection with Reestablishment of Continuity of the Common Bile Duct.* G. D. OFFENHEIMER. Ann. Surg. 116: 141 July 1942.

The feasibility of treating a malignancy of the extrahepatic bile ducts by radical surgery is illustrated by this case report. Exploration of a 57 year old man for painless jaundice revealed a carcinoma of the cystic duct as it entered the common bile duct. The gall bladder with cystic duct and a portion of the common duct were resected. Two large metastatic lymph nodes were removed from the portal vein. The common bile duct was reconstructed over a rubber T tube. His recovery was complete. The patient lived for eleven months, dying with evidences of hepatic metastases.

*A Revision of the Prognosis in Mongolism.* C. POTOTZKY AND A. E. GRIGG. Am. J. Orthopsychiat. 12: 3, July 1942.

The authors try to prove in 21 cases of Mongolism in a very thorough daily observation during several years that the usual unfavorable prognosis in Mongolism is not justified. They saw Mongoloids with average higher mental ages than supposed in the text books and especially the mean social ages of Mongoloids can be increased much higher by training than their mentality would seem to permit. This difference could reach even 6.9 years. The Mongoloids showed a mean social acceleration of one year and three months over the non-Mongoloid group. Generally unknown specific stigmata in Mongoloids were discussed. The term "Mongolian Idiocy" should be discarded and the term "Mongolism" be substituted.

*Primary Malignant Tumors of the Testicle.* P. ROSENBLATT, D. M. GRAYZEL, AND M. LEDERER. Am. J. Surg. 57: 94, July 1942.

A study of 29 cases of intrinsic testicular neoplasms gave support to the concept that essentially all these primary tumors are teratomatous in origin. The cases were sub-divided under the headings of homologous and heterologous tumors. The former embraced Ewing's "embryonal carcinoma" (seminoma) and the latter was frankly teratomatous. The heterologous tumors appeared in an earlier age group and offered a poorer prognosis than the homologous neoplasms. Trauma was reported in 10 per cent of cases. There are no pathognomonic signs of testicular neoplasm, but painless enlargement is the most common presenting symptom.

## BOOK REVIEW

*The Psychiatric Novels of Oliver Wendell Holmes.* Abridgment, Introduction and Annotations by CLARENCE P. OBERNDORF, M. D. Columbia University Press, New York, 1943.

It was fortunate that in the course of preparing a paper on "Oliver Wendell Holmes—A Precursor of Freud," Dr. Oberndorf found it desirable to read Holmes's three novels, "Elsie Venner", "The Guardian Angel", "A Mortal Antipathy".

These novels had been largely neglected both when they appeared and since. Their literary values had not been highly praised and Holmes was too far ahead of contemporary thinking for their value as psychological documents to be recognized. However, now re-examined by one skilled in the dynamics of behaviour, they have provided a wealth of fascinating insights into human conduct and have added to Holmes's great and lasting reputation as a clinician, an awareness of his equally fine skills as a psychiatrist. Psychiatry was in Holmes's day barely a specialty at all; the greater the wonder then to discover in Dr. Oberndorf's arresting presentation how much of the fundamental Freudian concepts was anticipated by Holmes and uniquely illustrated in the novels, here skillfully abridged to emphasize their sociological and psychological import.

As Dr. Oberndorf emphasizes, Holmes spoke of the unconscious with "understanding and eloquence." Thus he states: "Unconscious activity is the rule with the actions most important to life. The lout who lies stretched on the tavern-bench, with just mental activity enough to keep his pipe from going out, is the unconscious tenant of a laboratory where such combinations are being constantly made as never Wohler or Berthelot could put together; where such fabrics are woven, such problems of mechanism solved, such a commerce carried on with the elements and forces of the outer universe, that the industries of all the factories are mere indolence and awkwardness and unproductiveness compared to the miraculous activities of which his lazy bulk is the unheeding centre." Holmes also emphasized society's need to appreciate the role of unconscious motivation in behavior, especially in evaluating human conduct.

He also spoke significantly of another Freudian mechanism, the meaning of dreams: ("The cases are numerous where questions have been answered, or problems solved, in dreams, or during unconscious sleep. Two of our most distinguished professors in this institution have had such an experience, as they tell me. Somnambulism and double-consciousness offer another series of illustrations.") and touched on other problems which are still matters for psychological investigation. Among these Dr. Oberndorf mentions as significant "the quantity and quality of thought-flow—of the 'interval movement' of which we are wholly unconscious, 'when one idea brings up another'; the force of childhood memories; the unconscious factors in plagiarism; the function of censorship; the differences in the type of thought in males and females; the effects of sexual frustration in producing physical symptoms and character traits" and points out that "in his novels we find textbook examples of common psychoanalytic mechanisms such as displacement, sublimation, overcompensation, and the like." But, perhaps most important, this volume supplies an unusual textbook of psychiatry along entirely original paths and everywhere illuminated by Dr. Oberndorf's vast clinical knowledge and psychoanalytic insight. His annotations are models of clarity and stylistic felicity and present provocative and penetrating interpretations.

Each layman, student of literature, physician and psychiatrist may find a treasure house in this volume, but to no one will it prove more enlightening and helpful than to the student of psychiatry who quests for collateral reading. Here he will find it, delightful and instructive, and immensely rewarding. Many of these footnotes in a half dozen sentences say eloquently what pages of more formal psychiatry textbooks only render sterile. For instance, apropos the character of Lurida in "A Mortal Antipathy," Dr. Oberndorf adds:

"Most people would agree that masculine and feminine types of thinking are readily

distinguishable. The distinction finds popular expression in such phrases as 'he talks like an old woman,' or she has 'the mind of a man.' To the latter class Lurida would belong. Such a woman usually finds great difficulty in psychosexual adaptation, for the intellectual interest is of a type which interferes with the development of feminine characteristics. The disharmony between the 'masculine mind' and the feminine body predisposes to a schism in the personality. Clashes occur between the intellectual drive, unconsciously appreciated as manly, and the demands of society for contribution to strictly feminine fields of activity and endeavor. The conflict may lead to attempts at repression of the alien type of thinking and this mechanism in extreme cases may produce the feeling of not being oneself, estrangement, unreality and depersonalization."

This, a sample which must surely lead the reader to the original.

SOL WIENER GINSBURG.

## IN RETROSPECT AND A WORD OF THANKS

With this issue, the JOURNAL OF THE MOUNT SINAI HOSPITAL rounds out ten years of uninterrupted bimonthly appearance.

It had a modest beginning, not unembarrassed at first by doubts and apprehension as to how it would be received. However, the continued and encouraging growth of the number of its subscribers and the equally constant increase in the number of printed pages in each successive volume provide ample proof that those fears were unwarranted.

Aside from its readily demonstrable material growth, the Journal can rightly boast of many pages embellished by the names of some of the foremost men in medicine and of the pages carrying the remarkable William Henry Welch Lectures delivered at The Mount Sinai Hospital by J. B. Collip on *Some Recent Advances in the Physiology of the Anterior Pituitary*; by Sir Henry Dale on *Acetylcholine as a Chemical Transmitter of the Effects of Nerve Impulses*; by Walter B. Cannon on *Some Aspects of Homeostasis and Homeostasis in Senescence*; by Herbert M. Evans on *New Light on the Biological Role of Vitamin E*; by Peyton Rous on *The Conditions Determining Cancer and The Known Causes of Cancer*; by Homer W. Smith on *Renal Physiology Between Two Wars* and *The Application of Saturation Methods to the Study of Glomerular and Tubular Function in the Human Kidney*.

It is equally proud of the privilege of publishing the Edward Gamaliel Janeway Lectures which included: *Direct Action in Medicine* by the Rt. Hon. Lord Horder; *The Secretin of Bayliss and Starling and The Function of Thymonucleic Acid in Living Cells* by Einar Hammarsten; *Some Biologic Aspects of Protein Chemistry* by Max Bergmann; *The Nature of Clinical and Experimental Hypertension* by Irvine H. Page; *Newer Concepts of Infection and Immunity and Chemistry's Part in Their Development* by Michael Heidelberger.

The Journal can be well pleased with the reception accorded to its Anniversary Volumes, nine altogether, most conspicuous among which are those dedicated to B. S. Oppenheimer and Bernard Sachs, respectively Consultant Physician and Neurologist to The Mount Sinai Hospital. They are replete with contributions of signal and lasting value from men most prominent in the science and art of medicine.

By publishing the installments of the *Story of The Mount Sinai Hospital* on the occasion of its 90th Anniversary celebration, the deep interest of many a friend of the Hospital was satisfied. Covering the first fifty years of the Hospital's activities, the historical notations, carefully collected from the Hospital's records, other documents, and from personal interviews with "those who have been both eye-witnesses of and contributors to the Hospital's progress" give an interesting account of the origin and growth of the Hospital. To some extent they reflect "the way of medicine in New York and elsewhere since 1852 and the changing environment as a background."

To meet an insistent demand, the Journal brought to its readers carefully edited and well illustrated reports of the clinico-pathological and clinico-neuropathological and other conferences at the Hospital.

The recent publication of the first three *Essays on the Biology of Disease*, which on completion of a series of ten installments are to be assembled and issued as a monograph, is an innovation which has already stimulated other similar undertakings and holds out great promise for attracting more original and instructive material.

The Journal is also fortunate in having merited, beginning with its first issue, the right to join a distinguished company in the Cumulative Index Medicus of the American Medical Association.

On the whole it seems reasonable to say that, throughout the ten years of its existence, the Journal has carried out its projected purpose to present on its pages useful medical facts, old and new, in a language clear, concise, and as simple as the subject matter would permit.

Facts, though old, but therefore tested by time and experience, were in a way preferred, for it was felt that not *all* such facts were known to *all* and, moreover, when interpreted in a new light alongside newly observed phenomena, they acquire new and significant values. It was also realized that in medical science as in other disciplines, true knowledge can only gain by repetition and widespread diffusion.

The Journal came into being during dark days of the depression when rumblings of the approaching storm carrying with it hate and oppression were growing ever louder. In spite of the uncertainties of that day and the growing dislocation and confusion created by the subsequent tragic events, the Journal maintained a steady pace in its forward march. Now that the forces of destruction are checked and are about to be vanquished, as efforts to regain lost ground are about to begin, the Journal is fully prepared to join actively in the task.

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From its very beginning, the Journal found in the Board of Trustees loyal patrons who displayed their faith in this undertaking by granting its editorial management full autonomy of direction. No less helpful was the Director of the Hospital who was ever ready to extend to it a friendly hand.

The Journal is most grateful to members of the staff of the Hospital whose valuable contributions served as its mainstay and to the lay workers for their efforts in a sincere desire to secure the success of this educational medium.

Acknowledgement is due also to the Waverly Press and its officers for valuable advice generously given and for its excellent performances in the printing of the Journal.

JOSEPH H. GLOBUS, M.D.

## THE EARLY YEARS AND RAPID DEVELOPMENT OF NEUROLOGY IN AMERICA AND ITS RELATION TO MEDICAL SCIENCE. II.\*

BERNARD SACHS, M.D.†

[*New York*]

Let me refer to a few of the *more important topics* that occupied our minds in this Hospital four and five decades ago and in more recent years. Innumerable articles were written on one or the other aspect of syphilis of the nervous system. It is a long call since Mills, in 1888, wrote: "It is absurd to assert that locomotor ataxia is always due to syphilis as Erb has done," although Birdsall's statistics substantiated Erb's contention. The discussions were serious and thorough; in the end truth prevails and nowadays, with the wisdom gained by the Wassermann reaction and lumbar puncture, syphilis, as the chief causal factor both in tabes and general paresis, is universally accepted. Our scientific work at the Hospital deserves credit too for the critical judgment shown in the final evaluation of theories advanced and procedures suggested. It took only a few years to prove that while a positive Wassermann reaction indicated the presence of constitutional syphilis, a negative test did not exclude it. Just so, some years later, the Swift-Ellis treatment which promised at first to sweep us off our feet, was looked into critically and calmly and was less and less in vogue as the years rolled by, and not to the detriment of the patients. The lesson many of us learned was that however rational a therapeutic procedure may appear to be, any sort of interference with the brain or spinal cord should be weighed carefully to determine whether the procedure in question may not be productive of more harm than good. I am tempted to say that it might have been better if we had been more critical in the universal practice of lumbar puncture, and of the many endocranial punctures for purely diagnostic purposes; let us consider carefully the advisability of other surgical procedures before we favor frontal lobectomy as a cure for some forms of insanity. Let us remain conservative and critical, lest we jump from the frying pan into the fire. The same thought holds good for many other diagnostic and therapeutic procedures of these later days. I must not digress, however great the temptation may be.

Among the subjects that fascinated us early American neurologists were the progressive muscular atrophies. Here again the most important task was to establish definite types. Every effort was made to differentiate the amyotrophies from the progressive dystrophies, and among the latter to make Erb's type, the Landouzy Dejerine form, the old pseudohypertrophic type distinctly recognizable. Mills, Dercum, George W. Jacoby, contributed to the prolonged discussion of this subject. It may not be amiss to quote from a paper published just forty years ago by B. Sachs and Harlow Brooks with the report of an autopsy in a case of progressive muscular dystrophy. "The chief inference to be drawn

\* The first part of this paper appeared in the Alfred Meyer Anniversary Volume (Vol. X, No. 5, 1944) of the Journal of The Mount Sinai Hospital.

† Dr. Sachs ceased February 8, 1944.

from the negative findings of this case is that the spinal cord of a patient who had suffered for over fifteen years from a distinct form of progressive muscular dystrophy did not present any evidence to show that the wasting of the muscles could be attributed to disease of the gray or other matter of the spinal cord" (Am. J. Med. Sc., July 1901).

Even at that time some of us anticipated present day efforts in the hope that a small number of patients with progressive muscular disease may be rescued from the sad fate that awaits so many of them. Let us hope that the new chemotherapeutic endeavors may offer a brighter outlook than before.

Americans also took part in the problem whether the peroneal form of progressive muscular atrophy (the Charcot-Marie Tooth type)<sup>6</sup> belonged to the amyotrophies or myopathies. The general opinion decided in favor of a neuro- or neurospinal affection rather than a purely muscular affection. All this may appear to be a matter of some indifference to the present day neurologist, but we of that day devoted much time to these studies and helped to furnish a stable basis for further research in an important series of diseases.

A very good idea of the very gradual development of neurology in Europe as well as in America may be had from the earliest pediatric studies on infantile cerebral palsies. In 1842 Henoeh wrote on *de atrophia cerebri* describing the brain conditions associated with infantile cerebral diplegia. In 1860 Heine distinguished between infantile, spinal and cerebral palsies; before his day some of the older French authors had reported on atrophic changes in brains of children afflicted with various forms of palsy. In 1868 Charcot and his pupil Cotard wrote on partial atrophy of the brain.

Kundrat in 1882 published a fine monograph on porencephaly—a term introduced by Heschl. Bourneville, Pierre Marie wrote on lobar sclerosis. In 1884 Struempell attributed infantile spastic hemiplegia to an acute encephalitis, a polioencephalitis, not unlike poliomyelitis.

Then we Americans entered this arena. Among the earliest pioneers were Sarah McNutt, Peterson, Starr, Spiller, Osler and I may add Sachs, since my own publications go back to the year 1887; and I am given credit for having published the first textbook on Nervous Diseases of Children in 1895. It was my friend Dana who persuaded me to write it, and for fully half a century child neurology has been my special field of research.

In 1890, B. Sachs and Frederick Peterson published their fundamental studies on the infantile cerebral palsies—a sober analysis of 140 cases in which we established beyond dispute that these conditions were due to various factors and that at least three groups were to be recognized: 1) the prenatal; 2) the true birth palsies; 3) the acquired palsies, due to (a) acute and early infections, (b) to hemorrhages (infantile apoplexy). We contended that these palsies were not to be put in one basket; entirely different disorders may have some symptoms in common.

<sup>6</sup> Sachs was, so far as known to the present writer, the first American author to take part in this discussion. "Peroneal Form or Leg Type of Progressive Muscular Atrophy." Brain, 12: 447, 1890.

These conclusions have been generally accepted. One statement made fifty years ago has escaped general notice. It is difficult to explain acute cerebral hemorrhage in children, intracerebral and meningeal. "In his endeavors to elucidate this part of the inquiry, Sachs was compelled to fall back upon the fatty degeneration of the blood vessels which von Recklinghausen describes in his masterly monograph and which he claims is a not uncommon finding in the brains of children."<sup>7</sup>

Any review of American contributions must take cognizance of Ramsay Hunt's profound studies on diseases of the corpus striatum which gained additional significance after the epidemic of lethargic encephalitis. Joined to the contributions of C. and O. Vogt and of Bielschowsky, the pathologic anatomy of paralysis agitans was firmly established; and a few years later the importance of the striatal region in the development of the dystonias became evident. Such work as this showed that even to this day careful clinical classification in conjunction with anatomic and physiologic studies of the structures involved help in the real advance of neurology and neuropsychiatry.

It goes without saying that all serious and organic minded neurologists were close students of bacteriology and kept step with the development of endocrinology and within the last decade with the revelations afforded by biochemical and electrical research. *The revelations must not be accepted as gospel truth until sound critical judgment has approved of them.* Much is to be expected from the closer study of neuromuscular activity, from vitamin research and from electroencephalography; vitamin deficiency may be an important factor in some spinal disorders, but surely not the only one; there may be a definite electric pattern in epilepsy, but we have far to go before we have a right to claim that epilepsy is an electric dysrhythmia; it is surely much more than that.

The value of continued clinical research correlated with exact histologic studies has been impressed upon me by my own experience during the last 56 years. In 1887 I published my first paper on "Arrested Cerebral Development with Special Reference to its Cortical Pathology." My chief interest was in the cellular changes which Van Gieson and I found in the brain of a child. This patient was seen by me after I had been associated less than two years with an eminent general practitioner. "Just an ordinary case of idiocy," said my senior. "No", said I, "a most unusual combination of symptoms." But in those days a junior had a hard time standing up against a man of huge experience. However, I stood by my guns and a few years later came across a second case in the same family and generation and only nine years later did I establish the type and called it Amaurotic Family Idiocy. Since then others have called it Tay-Sachs Disease, *Waren Tay* having described the retinal changes. Later on, Spielmeyer, and the Vogts differentiated a juvenile form from the infantile group. While the two types had many symptoms in common, there were also distinct differences between them. Had we not guarded the types carefully, there would have been great confusion. For years and years I thought I had

<sup>7</sup> Quotation from *Nervous and Mental Disorders from Birth Through Adolescence* by Sachs and Hausman, p. 238, where those interested may find many other details.

described the disease well enough since no one added or detracted from the clinical and earliest pathologic facts as established by a host of workers including Schaffer, Globus, Hassin, Strauss and myself. For years I was fairly satisfied with the belief that I had done all that could be expected of me. Lo and behold! During the past decade Epstein of Vienna, L. Pick and Bielschowsky in Berlin, corroborated by others, convinced me of the close relationship between this disease and Niemann-Pick disease; and after inspecting Pick's specimens in Berlin, I was convinced that in all these forms, a faulty lipid metabolism was the important underlying factor. I have the firm impression that when this morbid process is exhibited in all the important organs of the body, you may call it Niemann-Pick disease; when the changes are restricted to, or involve chiefly, the central nervous system, you may call it Tay-Sachs disease. Many other questions have arisen. Epstein, for instance, claims that the lipids in the two diseases are chemically different, but as I said in a previous (private) publication: "I am still fascinated by the thought that all these forms are related and the problem remains: how can faulty lipid metabolism be linked up with a family affliction?"<sup>8</sup>

"Let the present day investigator determine whether or not the endocrines have anything to do with the chemical processes. Still more important is the query which has been foremost in my own mind for a number of years—is there no way of meeting, diminishing or counteracting this faulty fat metabolism? I am full of hope that some day a physiologist or biochemist, or some young neuropsychiatrist with an active brain, may find the key to this problem, and anyone who will enter the arena successfully against the incurability of hereditary and family diseases will have everlasting fame." That it can and will be achieved, is my hope and belief.

Let me remind the reader again that while the chemist, the endocrinologist, the physicist have given great assistance, it remains for the *clinical neurologist to develop and present the specific research problems.*

Fortunately, our clinical studies have stood the test of time, or else all sorts of heterogeneous forms of disease would have made the problems still more complex than they are.

The further question arises, even though the predominant racial occurrence cannot be denied, may not environment as well as heredity play a part. Still other purely clinical problems arise.<sup>9</sup>

Let me urge the point that the chemists and electrophysicists, working with the clinician, should try to grasp the medical problem, or at least to develop a sympathetic interest. It has been especially gratifying to me that my long continued interest in this one disease has led to research on many fundamental problems relating to heredity, environment and the causes of supposedly hereditary diseases.

<sup>8</sup> These and other quotations are from an address (privately published) on "Present Day Trends in Neuropsychiatric Research" read before the Bellevue Neurological Conference on March 17, 1939.

<sup>9</sup> Those interested in these problems may find my present day views in a paper submitted to the Third International Neurological Congress in Copenhagen (read by Dr. Riley) August, 1939.

Abner Wolf's writings on toxoplasmic encephalomyelitis have made me<sup>1</sup> suspect that among congenital disorders, there may be a number due to some infections or other intrauterine process; and surely in no way truly hereditary.

Neurology and modern neurophysiology profited much from the clinical and anatomical investigations of problems related to brain tumors. Here the American school of neurosurgery led by Harvey Cushing and the American "studies on the pathology [and related clinical manifestations] of intracranial tumors, begun by Globus in New York and by Bailey and Cushing in Boston . . . extended by Penfield, by Alpers and many others,"<sup>10</sup> opened an important and fruitful field of research. With the development of modern neurosurgical technique, more aggressive and less hazardous steps became available. This, when coupled with the newly acquired knowledge of the biologic character and behavior of brain tumors, made it possible to approach such problems with a better understanding of the probable advantages or certain disadvantages of surgical intervention. But what is equally important is that the comprehensive studies of cerebral neoplasms have contributed much to the general pool of knowledge of the physiology of the brain and have thereby thrown much light on other neurological questions.

Within recent years the chemistry of the brain assumed special importance in the discussion of mental and nervous disorders. Quoting again from a previous address: "As I see it, we neurologists, and neuropsychiatrists, especially those of us who have adhered to orthodox doctrines"<sup>11</sup> (and the majority have) will have our forces well in hand for the impending battle. *The struggle is to keep neurology and neuropsychiatry on a sound organic basis and to clarify the fundamental processes governing the activities of the nervous system.*"

Beyond a doubt, the startling disclosures of Manfred Sakel regarding insulin shock treatment gave a tremendous fillip to this line of inquiry, and we find ourselves only at the beginning of an entirely new line of investigation. Great care will be needed before we reach definite conclusions as to insulin and still more as to metrazol. Without attempting to take up the cudgels in this debate, let me refer to Himwich's very apt simile: "To contrast the fundamental differences of the action of metrazol and insulin, the latter decreases the amount of coal (glucose) necessary for the fire to support cerebral function, while metrazol interferes with the draft (oxygen) required to maintain the flame. The end-results in regard to the supply of energy to the brain are the same with both methods."

"Not all those especially interested in these problems appear to realize that after metrazol injection, the inhibition of cerebral metabolism is due to acute anoxemia, and this in turn is induced by the severity of convulsions and the temporary arrest of respiration."

If this be true, the anoxemia of a similar degree produced by any other means

<sup>10</sup> Bailey, P.: The present state of American neurology. *J. Neuropath. & Exper. Neurol.*, 1: 112, 1942.

<sup>11</sup> It might interest even his followers to know that in a letter written to the present writer (dated London, July 19, 1938) Sigmund Freud said: "Fortunately, I have not been hostile to (*nicht verfeindet bin*) organic neuropathology."

should be equally effective. The attempt has been made to induce anoxemia by placing patients in an atmosphere in which the nitrogen was increased at the expense of oxygen. Wherever such investigation is carried on, there must be the closest collaboration between the clinician and the laboratory worker. One mystery remains: After either form of shock treatment, if successful, the normal cerebral activities remain, but the morbid processes are diminished or lost. What a fruitful field for further original research on the part of clinician and chemist!

There are other clinical problems pressing for solution regarding the action of acetyl choline, prostigmine, quinine and other substances that seem to have a direct bearing on the peripheral nervous system. As I said to a distinguished physiologist in Boston a few years ago: "From now on we had better drop our old jargon about the transmission of motor impulses, and begin to think of these functions in chemical or electrical terms." And that leads to a few concluding thoughts on electrical research that promises so much for the future toward clarifying brain activity.

The present day interest in these electro-potentials in the living brain was aroused by Berger's publications in 1929 and furthered by Adrian, Gibbs, Davis, Lenox, de Bareene and a number of younger men here in New York; at Bellevue, The Mount Sinai Hospital, the Psychiatric Institute, the Neurological Institute, and the Montefiore Hospital. Do these electrical impulses originate in the brain cells or tissue?

A number of points have been well established, but we must be most careful not to arrive at any hasty conclusions. That the potentials are actually derived from the cortex and are not merely part of general cerebral activity has been proved by de Bareene and McCulloch<sup>12</sup> who have shown, by gradual destruction of the cortex through heating, that the alpha rhythm disappears if all the layers are locally destroyed. In 1939, I wrote: "Adrian and Matthews believe that the presence of the alpha rhythm before stimulation is taken to imply synchronized discharge in a group of cells. The visual stimulus is said to stimulate a specific pattern among these cells and so break up the synchronized action, consequently the alpha rhythm disappears."

On the other hand, listen to what Berger has to say. He regards the alpha rhythm as a resultant of activity in a large mass of cells of the cortex as a whole. Apparently a specific sensory stimulus stirs up one special cortical area and inhibits activity in all other parts. In other words, Berger believes that the depression of the alpha rhythm reflects this process of inhibition in the greater part of the cortex. There is good reason to believe that there is independent electrical activity of the brain which is continuous but easily upset and inhibited by sensory stimulation. But is not sensory stimulation of some sort almost continuous during the waking state?

I have not the right nor the intention at present to go into the details of this electric research. I am trying merely to indicate how interesting and important, how fundamental these electrical investigations promise to be, and how much there is reason to believe our knowledge of brain activity will be affected once

<sup>12</sup> J. Neurophysiol., 2: 319, July 1939.

we have the right to draw definite conclusions. Before such conclusions can be reached, we must have the fundamental data to rely upon. It seems of the utmost importance to establish the electrical potentials of children at various ages before we can claim that this or that electrical pattern denotes early epilepsy or early manifestations of an impending mental storm, a manic depressive psychosis, or a schizophrenia.

The troublesome problems of epilepsy, of convulsions, will receive the closest possible attention, and if any further proof were needed, it is evident that psychiatry as well as neurology will have good reason to resort to these newer electrical methods in many of the special problems. While the insulin shock therapy of dementia praecox is well within the domain of chemical research, it will also be advanced by these newer electrical methods. There is the hint through careful studies of the convulsions following metrazol injections that we may be able to learn more about the exact changes occurring in the brain before, during and after convulsive seizures. Even in cases when there is the failure of an overt seizure after metrazol, interesting data have been secured and differences have been discovered from the findings when an overt seizure occurs, and again when the patient passes through the post-convulsive relaxation period until he returns to normal.

If I may continue in the line of mentor, let me urge caution in another direction. In studying the effect of radiation applied directly to the brain and spinal cord experimentally on monkeys, Elsberg, Dyke and Davidoff<sup>13</sup> found that large single doses of roentgen-rays applied directly upon the brain were followed almost immediately by contralateral hemiplegia. When one cerebral hemisphere was irradiated, both the homolateral and the contralateral hemispheres were involved, the latter much less than the former. When large doses of radiation were applied to the cerebrum, chromatolysis of ganglion cells of the cerebellum occurred similarly when the cerebellum was thus irradiated, degeneration of ganglion cells of the cerebrum was found. The effects of massive doses of roentgen-rays were especially marked in the glia and nerve tissues, but the changes in the blood vessels were slight in degree.

When smaller dosage was used and when one part of the brain was irradiated, distant parts of the brain when examined months later were found altered. These facts must be borne in mind when, as proposed by Marburg and others, small doses of irradiation are to be used over long periods in the treatment of hydrocephalus and other conditions. This important finding regarding the later effects of small doses of irradiation could only be determined by most careful pathologic and histologic studies of the old type. I repeat, therefore, that you cannot afford to neglect the old methods.

I realize that I have mentioned only a few of the large number of topics discussed by the active neuropsychiatrists and neurosurgeons, who during the last three decades have made prominent contributions to the advance of organic neuropsychiatry. I have been able to allude to only a few of the men and women in this country who have given neurology in America a secure place in the esteem

<sup>13</sup> Radiology, 31: 451, October 1938.

of the entire world. Let me close with remarks I made to a friendly group two years ago:

Pardon the young optimist. I would like to begin my career all over again. And if I could, I would first of all take up the study of the specific influence of each and every endocrine gland. Carefully directed research is needed, and since we have already learned to promote the normal and correct the abnormal physical growth of the child and to influence important functions of the body, we may some day find the clue to the correction and prevention of supposedly hereditary (family) mental afflictions. There is no field that offers greater opportunity for original fruitful research in the solution of innumerable problems than does organic neuropsychiatry.

## THE MATERNITY SERVICE OF THE FUTURE WITH SPECIAL REFERENCE TO THE MOUNT SINAI INSTITUTE OF BIOGENETICS<sup>1</sup>

I. C. RUBIN, M.D.

I feel deeply the privilege of being able to address the Board of Trustees of The Mount Sinai Hospital, at the invitation of Mr. Kops, on the subject of the Maternity Service of the future, a matter of such vital interest to the hospital and a matter of equal importance to the whole medical staff. The need of a maternity service has been felt not only by those of us who are directly and intimately concerned with problems in obstetrics and gynecology, but also by all the other services of the hospital in which the points of contact with such problems are not so immediate. It is felt by all that a hospital to be complete must provide for the care of women in their active reproductive period of life as well as at all other stages. Obstetrics of today is as much a part of medical practice as surgery, general internal medicine and all the other specialized departments. In connection with and as a part of the overall functions of a general hospital such as ours the urgent necessity of a maternity service obviously requires no further emphasis.

I shall not venture into a discussion of the reasons why the department of obstetrics has not heretofore been provided in the scheme of The Mount Sinai Hospital throughout its long career. I shall instead point to the fact that there is now manifested a very earnest and vigorous interest in the inauguration of a maternity service on the part of the Trustees and this, I can assure you, is welcome news to the members of the Medical Staff, particularly those whose practice is concentrated in this field.

One other thing we may be sure of and that is The Mount Sinai maternity building will represent the best in modern hospital construction, it will have the most practical architectural design and will contain all the most up to date equipment which has been found to be essential for the efficient, safe and satisfactory care of obstetric patients. From what I have observed of Dr. Turner's painstaking and meticulous plans there will be included every last provision that has been thought of by the most experienced hospital architects, designers and builders. For our own specific needs much has already been established by Dr. Turner's predecessor, that master architect and builder of hospitals, who has shed lustre on the name of Mount Sinai.

If we include and adopt all the activities commonly engaged in and considered as essential to the conduct of a maternity service we shall have a maternity service of the past and the present but not of the future. Mount Sinai has always been ready to adopt new measures in line with advances in medical science and art and we may speak with pardonable pride of our own contribution towards med-

<sup>1</sup> Presented at a meeting of the Board of Trustees of The Mount Sinai Hospital, January 11, 1944.

ical progress. What I should like to propose is I believe in keeping with this tradition.

Since we are dealing with a maternity service of the future it should necessarily be considered from a long range viewpoint. We have come a long way from the hospital for custodial care of lying-in patients. Though progress in obstetrics has not quite kept pace with the amazing advances in physics and chemistry, advances that have been reflected in modern industrial arts, nevertheless many improvements in obstetrics have been recorded in the past fifty years to warrant a recasting of our thoughts in this direction. Obstetricians of today may be said in a sense to be as far apart from the horse and buggy doctor as aeroplanes and radar are removed from the stage coach and covered wagon, so that it is timely to reformulate our notions about what constitutes a maternity service of the future.

To my mind such a service should have a fourfold purpose and function. The first is maternity care in the most modern and comprehensive sense of the term for expectant mothers throughout pregnancy, childbirth and during the lying-in period. This we may be sure will be provided for in accordance with the high standards maintained by Mount Sinai for all the patients that come under its care.

The second is education and training of interns, residents and nurses and other personnel who have to carry out the practice and art of obstetrics. The first and second are necessarily limited by the number of mothers and newborn children that can be accommodated in the hospital.

The third is research—clinical, biochemical and experimental. This is a function of the maternity of the future which must be particularly stressed since it is the one branch which enlarges the horizon of the others, increasing the scope of the maternity service well beyond the limits of location and community. An obstetric bed can be occupied by but one mother but the scientist's mind can generate many ideas which are not limited by space or time.

The fourth is social service which may be enlarged to include a number of educational features and other useful agencies not ordinarily considered in this connection.

A maternity service that comprises these four aspects may well be designated as a maternity center or better an Institute of Biogenetics since it is concerned not only with the principles and practice of obstetrics but with all the biological facts that go to make up the science of birth.

For a long time The Mount Sinai Hospital could be counted in the forefront of the most important hospitals in New York City and the United States and has earned an enviable reputation for contributions to medicine and surgery although the physicians of the hospital were for the most part on an entirely voluntary basis. We must now however face the fact that we are compelled to keep pace with the advances in organization which medical centers and other foundations with their large endowments, and pharmaceutical houses with enormous financial resources have in recent years established for themselves and thus have set a pattern for hospitals in general. The disparity in financial re-

sources has been responsible for the fact that we have not been able in recent years to meet the new demands for research. This is the urgent and imperative task which Mount Sinai Hospital must meet.

These increasing demands for the enlargement of the scope of the maternity service of the future may be satisfied by the establishment of a Mount Sinai Institute of Biogenetics, an institute which would offer opportunities for fundamental clinical and biochemical research to far-sighted, scientifically minded obstetricians and other physicians. The creation of such a maternity center would be a pioneer enterprise and a contribution of major importance to future obstetrics. It is the one thing that will differentiate our proposed maternity building and service from just another maternity building serving a given locality or even a somewhat larger community. The integration of the four activities of such a maternity service would constitute a departure in the field of obstetrics which would in the future embrace a wider sphere of influence, national and eventually international.

A survey of medical literature shows that but few maternity lying-in hospitals and fewer obstetric services in general hospitals have made noteworthy contributions to the progress of science. In most cases they were in the nature of small improvements of obstetrical technique, only few of which have permanent value. Obstetricians who are not satisfied with this limited field of research and who try to get a deeper insight into the miracle of the creation of man are compelled to look to various other places, mostly institutions dealing with theoretical problems if they wish to put their ideas to the test by trial or experiment. But it is not always easy to get such an opportunity and at best it involves a great loss of time and energy. Very often the chief of such an experimental institution has no real interest in obstetrical problems and, as a rule, possesses no clinical experience and critique.

In our hospital the central laboratories are ably staffed and the routine work is done in an efficient manner. But as far as research work is concerned the facilities are as you know cramped and there is need for much enlargement.

The organization of such an institute which I envisage would remove these obstacles and would enable the staff of physicians to carry on scientific work under favorable circumstances. I should like to give you in brief some idea of the work that needs to be done in such an institute of the future. I shall mention only a few of the problems that await solution.

(1) The first undertaking would be concerned with biochemical problems in the field of physiology and pathology of pregnancy, childbirth and the lying-in period. In pregnancy and after childbirth there take place great changes in the metabolism of the body. These changes serve a double function designed to keep the mother's organism healthy and strong while a new organism is being developed, i.e., the baby whose needs are not necessarily subordinated to those of the mother. On the contrary, the organism of the pregnant woman has to adapt itself to the requirements of the young without suffering serious injury. The unborn child lives in the truest biologic sense a parasitic existence growing at the expense of the maternal host. Whether the expectant mother is aware

of this or not she is practically almost always quite willing to be the host to this temporary parasite in the hope of seeing it born and grow up and develop into an independent human being. While the growing embryo may be said to snatch its foodstuffs in a form adequate for its development with utter disregard for the requirements of the mother's organism, the mother must be protected by all the knowledge and means that obstetric science and art can offer her.

Since the pregnant woman is in a state bordering on health and disease she needs special care and attention to maintain her healthy balance. Moreover, in many respects the organism of the mother has to be accommodated to that of the unborn child so that it may not be harmed. We have learned for example that the pregnant woman retains more water in her tissues than the non-pregnant woman. The result is that her cells are subject to the same conditions as those of the fetal cells which contain large amounts of water. An excess of water retention in the mother's tissues may provoke serious disturbances such as hydrops (water logging) and eclampsia (convulsions). The late Dr. Joseph De Lee has provided a niche in his Hall of Fame in the Chicago Lying-in Hospital for the discoverer of the cause of eclampsia. We may well set such a task for ourselves in the new maternity service.

If the nutrition of the pregnant woman is inadequate, various manifestations of deficiency disease such as polyneuritis, hemeralopia (night blindness) keratomalacia (softening of the cornea), scurvy, etc., may develop. The cause of toxemia of pregnancy, its prevention and cure; the cause of nausea and vomiting, annoying symptoms of pregnancy, are other obstetric disturbances that can be better studied in an institute of the type proposed for the maternity service of the future. Not unrelated is the fact that the organism of the mother in general and more especially the reproductive organs and the pelvic joints, have to undergo important changes in order to make the process of delivery possible. Through the unprepared birth canal a delivery would be impossible.

Thus, it is of great practical and scientific importance to study thoroughly the various changes of the metabolism of pregnancy and the nutritional requirements for mother and child. A better understanding of nutrition in pregnancy has already been gained thanks to advances in our knowledge of obstetric science during the last few decades and there is still room for much work of the utmost importance to be done.

The study of fetal metabolism is still in its beginnings due to technical difficulties involved in such investigations. The metabolic processes of the fetus in an environment poor in oxygen differ essentially from that of extrauterine life. The investigation of fetal metabolism has more than theoretical interest. Its practical purpose is to enable us to prevent many miscarriages and premature births, to secure the development of better and stronger babies, and prevent the occurrence of some fetal malformations.

(2) The Institute of Biogenetics should be concerned with a variety of hormonal problems. The function of the gonads, the maturation of the ova and spermatozoa, the embedding of the fertilized ovum in the uterus, its breeding and all the metabolic processes mentioned above. Labor and breast feeding

of the newborn are under the rule of hormonal organs. Within a comparatively very short time, endocrinology has grown into an important and extensive branch of medical science. Particularly in the field of gynecology and obstetrics great strides have been made. I need only remind you of the famous Aschheim-Zondek pregnancy test, of the knowledge of the function of the corpus luteum, the placenta, and the hypophysis. Many endocrinological problems have been solved, many more await solution. Endocrinologic studies would be best carried out in such an institute where the material lends itself admirably to biogenetic research.

(3) Serological research in obstetrics has been pushed into the background in favor of endocrinologic work during the last decades though we owe to it the knowledge of some interesting facts concerning parallel reactions in pregnancy and malignant neoplasms and about the transition of immune bodies from the mother to the fetus. That serology also promises to furnish new facts is illustrated by the amazing story of the Rh factor which was discovered by Landsteiner, Wiener, and Levine and encountered in about 85 per cent of the population. Abortions, miscarriages and serious illnesses (erythroblastosis) of the newborn child may be the consequences of the unhappy association of two otherwise normal and healthy people. The determination of the Rh factor before marriage may prevent the fatal consequences of such a pregnancy. If a man with a positive Rh factor marries a woman who also has a positive Rh factor, nothing wrong will develop from the mixture of paternal and maternal elements in the offspring. The same is true if both parents are Rh negative. But if the husband is Rh positive while the wife is Rh negative, it may happen that the fetus will inherit the Rh factor from his father and by transition of this factor into the maternal blood will induce the formation of antibodies against the mother's Rh factor. These antibodies pass through the placenta into the fetal circulation and may injure the fetus seriously and even kill it.

(4) An institute of biogenetics will include all problems concerning reproduction. This comprises the large field of sterility, its causation, prevention and cure. The husband as well as the wife can be responsible for a childless marriage. The male sterility can be caused by lack of spermatozoa in the ejaculation due either to non-formation of spermatozoa in the testicle because of cryptorchism, eunuchoidism, etc., or due to an obstruction of the seminal ducts. It may be further caused by inviability of the spermatozoa, through damage of the spermatozoa from a disease of the prostate or the seminal glands. A woman may suffer from sterility because she has no fertilizable ova or because her Fallopian tubes are obstructed. Other factors that militate against conception are inadequate preparation of the uterine mucosa for the embedding of the ovum, destruction of the spermatozoa in the cervical mucus, expulsion of the semen from the vagina and many other unestablished factors. The diagnosis and the treatment of all the factors involved in involuntary childlessness represents a wide field of research which is very interesting and important, but also very difficult under restricted facilities available at the present time.

Artificial insemination has recently been brought to public attention in a

sensational manner. It has its proper place in cases where natural insemination is impossible because of a defect of the husband. Artificial insemination has already interested gynecologists for a long time. After many serious disappointments some success and some promising results have been obtained and we hope that the results of artificial insemination will become as good in man as they are in animals. To find out the reason for the usual failure of artificial insemination in man and to remove these impediments is an important object of the Institute of Biogenetics.

(5) We still do not know how the human ovum matures, how it is taken in by the tube, how it is carried through the tube into the uterus, how long this migration of the ovum lasts, how long the mature ovum and spermatozoon remain viable and fertile, what is the real duration of normal pregnancy, i.e., how long it takes from the conjugation of the ovum and the spermatozoon to the date of delivery; what initiates and causes labor, etc. There arise innumerable highly interesting problems, many of them also of practical value. For instance, the question of the cause of ectopic pregnancy is in close connection with some of the subjects above mentioned. The solution of these problems requires the careful and critical combination of experimental, clinical and histological studies.

(6) A maternity service provides the material for research in embryology, in heredity (e.g., research of twins) and eugenetics. The study of heredity and facts resulting from such study form the basis of practical matrimonial consultation and represent a field of research work of steadily increasing importance.

(7) The obstetrician unfortunately is sometimes compelled to interrupt a pregnancy in order to save the life and the health of the pregnant woman. The question when such an interruption of pregnancy is necessary, has to be revised again and again because progress in medicine will restrict more and more the cases where such an operation is inevitable in the interest of the pregnant woman.

(8) Better than to interrupt the pregnancy and destroy a new life, is to prevent undesirable pregnancy. How to manage it best and with the greatest possible security, is an important problem to be studied in the biogenetic institute.

There are many other problems that deserve attention. I shall mention but a few: (a) The biological chemical immunological character of spermatozoa. Their generative aspects, methods of prolonging their longevity and viability. Steps have already been inaugurated at this hospital but the work which appears to be encouraging has only begun. It will require years of painstaking research under the best auspices as those in an Institute of Biogenetics to solve these problems. (b) Improvement in methods of artificial insemination by addition of various buffer and nutrient media, etc. (c) The recovery of human ova, their longevity and viability and impregnation in vitro. (d) The recognition of factors that enter into defective germ plasm and the cause of monstrosities. (e) The mechanism of labor inclusive of the functions of the muscular apparatus of the pelvis awaits full elucidation. Some steps have been taken elsewhere in anticipation of this work but under difficult conditions and less favorable auspices. (f) Factors that enter into the determination of sex. (h) Safe

methods of painless childbirth. (i) Reduction in morbidity and mortality in obstetrics.

To fulfill all these tasks the Institute of Biogenetics requires accommodations for (1) physiological and biochemical, (2) endocrinological, (3) embryological and histological, (4) serological and hematological, (5) radiological and (6) experimental and pathologic-anatomical research work.

It would also be desirable to have a special fund to finance research work which coworkers of the maternity center cannot do but which can be carried out in certain special institutes (as in botanical, zoological, marine laboratories, etc.). Funds for fellowships to support qualified and desirable interns and residents on completion of their services would go a long way to develop the scientific work of the maternity service of the future.

The serological laboratory should be combined with bacteriological accommodations sufficient to grow cultures of gonococci, and other organisms, as well as to carry on other bacteriological work essential for the care of pregnant women and parturients.

As to the second departure from the past in connection with social service of the future maternity service, special attention should be given to the human relationships which concern sex education and childbirth. For several of the items I am indebted to Dr. Robert L. Dickinson, pioneer and masterful exponent of the principles governing control of conception. They are incorporated here as an integral part of the social activity of a maternity service.

- (a) Sex education for adolescent girls.
- (b) Premarital examination and counsel.
- (c) Postmarital advice and adjustments with reference to sex life and health (conjugal hygiene).
- (d) Advice as to planned parenthood and best methods of contraception for health purposes in suitable cases.
- (e) Determination of better indications for interruption of pregnancy and for sterilization and best methods for each.
- (f) Instruction in child care before and after childbirth.
- (g) Psychiatric study of the obstetric patient and preventive child hygiene, mental and physical.
- (h) Eugenics and eugenics and family relations.
- (i) Child adoption.
- (j) Problems of population which may arise directly or indirectly from the general survey of the work done in such an institute.

The care of the obstetric patient during pregnancy, labor and delivery of the newborn child and during her lying-in period occupies the mechanics of the ordinary maternity service. The Institute of Biogenetics would deal with the fundamental problems of fertility and of sterility inclusive of all the many biological problems that go to make up the prerequisites of conception. On the other hand the aforementioned social services which have arisen from modern living may, properly speaking, come under the aegis of the maternity service of the future.

A few words only about one of them, namely, child adoption. This activity

is ordinarily conducted by separate agencies not connected with a maternity service. Hitherto unrelated to the functions of obstetrics, it is a most worthy service offering refuge to desirable parenthood when the efforts of science in the last analysis fail to restore fertility. It is a vicarious satisfaction for such parenthood that is denied natural biological self-fulfillment. Incidentally in my opinion it is the highest expression of social and humane service creating the best good will for the hospital which engages in this humanitarian work. Child adoption is usually resorted to when all else has been tried. In connection with a maternity service of the kind here envisaged the foster parents will at least have the feeling of assurance that they have had the full benefit of all that biogenetic science can offer under the most favorable circumstances both for themselves and for the child which will be adopted. Incidentally proper psychiatric guidance can be provided to such parents for sane and natural filial relationship.

A few words also with regard to one phase of eugenics which has not been systematically studied, namely, that of the mental and physical growth of the child in relation to the type pregnancy and the kind of labor and delivery which the mother had in bearing her child. This is a work in which the pediatric and psychiatric departments can cooperate in the maternity service of the future and make a notable contribution to society.

At this point, as a brief historical note, I would like to recall that Mount Sinai has a unique record of achievement in the progress of the investigation in a related field, the cause and relief of sterility. By some curious turn of fate it has contributed some of the major discoveries in this field. The first important contribution was made by Emil Noeggerath who was appointed gynecologist to Mount Sinai Hospital in 1877. There had been no gynecologist in the hospital before him and his services were limited to the Out-patient Department as gynecology was not yet separated from general surgery and medicine. Noeggerath has the credit of being the first to call attention in 1872 to the sterilizing effect of venereal disease upon women. Seven years before the cause of gonorrhea was discovered by Neisser, Noeggerath pointed out that this infection attacked the Fallopian tubes which became sealed and therefore shut out the prospects of conception. Noeggerath's second contribution to the science of sterility was truly astounding though it should have occurred to physicians long ago namely that the male can also be sterile as a result of the same disease. Thus he drew attention to the importance of considering the male partner in the causation of sterility. His work and teaching are responsible in the largest degree for the removal of the stigma that had been attached to the female alone, a stigma that branded her from time immemorial till the end of the last century.

In the early part of the present century one of our Clinic chiefs, Max Huhner, made the third important contribution. He called attention to a simple biological method whereby not only the mechanical potency of the male was demonstrable but also to a certain extent his generative ability as well as the interaction of the genital secretions. His work became known as the Huhner test and is still employed by many gynecologists.

The fourth important contribution was made by Robert T. Frank whose pioneer work concerning the nature, quality and quantity of female sex hormones during the menstrual cycle and pregnancy paved the way for much of the work that has been done in the past 15 years or more in the field of hormonology. As his work is more familiar to you I shall not enter further into it. Suffice it to say that it has been recognized all over the world and Mount Sinai may be truly proud of this achievement also.

The fifth contribution to the field of sterility dates back to 1919, almost a quarter of a century, when the method of uterotubal insufflation was devised at Mount Sinai Hospital. This method had as its object the clinical non-surgical determination of the fact whether in any given woman who cannot bear children, though she does nothing to prevent conception, the failure to conceive may not be due to blocked tubes, an abnormal condition which makes it impossible for the male germ cells (spermatozoa) from meeting up with the female germ cells, the ova.

It is of historic interest to note that previous attempts made elsewhere by others besides myself with x-ray opaque solutions to arrive at a non-surgical method to determine whether the Fallopian tubes are open or closed had not been satisfactory. This method known as uterosalpingography became more serviceable after the insufflation method with carbon dioxide gas which was developed at Mount Sinai became generally adopted. The test derived importance from the fact that up to the time of its inception it was not possible safely to tell whether a woman could conceive without cutting open her abdomen and inspecting and probing the Fallopian tubes. This was a formidable thing to do for a diagnostic investigation which has since been made possible without the hazards of an operation and carried out within one or two minutes.

Mr. President and Ladies and Gentlemen: In the short time at my disposal I have attempted to outline the scope and program of the maternity service of the future indicating some of the problems it will be the task of The Mount Sinai Institute of Biogenetics to solve. There are naturally many more problems than I have had time to enumerate and it is expected many more will arise in the course of time. It is the spirit of such an Institute of Biogenetics which will give substance and inspiration to the maternity service. I am confident that under the management Mount Sinai Hospital is fortunate in having, the proposed maternity service can and will make its contribution to the science and art of obstetrics as it has already made in medicine and surgery during nearly a century of its existence.

## TRICHOBEZOAR

DAVID MILLER, M.D., AND MORLEY KERT, M.D.

*[From the Surgical Service of Dr. Ralph Colp]*

There are three cases of trichobezoar listed in The Mount Sinai Hospital records. The rarity of the condition is readily appreciated and in DeBakey and Ochsner's excellent review published in 1938, only 172 cases of trichobezoar were collected.

The term bezoar refers to a concretion of various character from animal stomachs and have long held a fascination for medical therapeutists because of the extraordinary powers attributed to them by the ancients. A treatise on their value was written by one Imad-Ol-Din as early as the seventeenth century. They were considered to be of great value as antidotes to poison, for the restoration of lost sexual powers and for the cure of a wide variety of illnesses. A bezoar stone was used by no less a personage then Governor John Winthrop of Massachusetts. An idea of their value at that time is apparent from the fact that they were listed among the crown jewels of Queen Elizabeth.

The term trichobezoar refers to hair ball in the stomach or other portions of the gastro-intestinal tract. Phytobezoar is a term reserved for concretions consisting of vegetable, fibers, skins, leaves or stems. These masses are usually impregnated with fats, fatty acids, starch granules and the like. Seventy-five per cent of the phytobezoars are caused by the persimmon fruit. The latter is such a frequent offender that a separate name, Diospyrobezoar, has been suggested for this type of concretion. The term Diospyrobezoar is derived from the Greek Diospyron, translated as "Jove's Grain", and refers to the variety of persimmon most frequently responsible for the concretion.

Persons drinking furniture polish and using water as a chaser are subject to the formation of a ball of shellac in the stomach, formed by the precipitation of the shellac from its alcohol solvent.

In addition to those masses brought about by chemical and physical changes there are also on record cases of gastro-intestinal obstruction due to boluses of food such as skins and stems of grapes, prunes, raisins, celery fibers, orange pulp, etc. There is quoted, no less, the experience of one misguided individual who drank raw latex, thereby constructing an accurate latex cast of his stomach.

In the cases of trichobezoar where sex was noted, 139 were female and 13 were male. All the cases in this hospital were female. It would seem from this that the condition and habit of eating hair, i.e., trichophagia, is more common in the female, possibly because of the longer hair. When, however, the incidence was listed by decades, and the long or short hair style of the decade is noted, no significant variation is apparent.

In contrast to the preceding, there is roughly a 3 to 1 incidence of male to female in the case of phytobezoar.

The most frequent occurrence of trichobezoar was in the period between

the ages of 10 and 19 years. In phytobezoar the maximal number of patients were between 50 and 59 years of age.

The ingestion of incredible substances is not uncommon in the frankly insane, in pregnancy and in uncinariasis. In recorded cases of trichobezoar only about 14 per cent were said to have shown some obvious mental abnormality. This aspect of the problem is as difficult as it is interesting. The line dividing normal taste from the unusual is exceedingly tenuous and the gastronomic adventures of one individual may be utterly bizarre to the next. There is no doubt, however, that despite variation in dietary habits, the eating of human hair, is universally regarded with repugnancy. In the reports, no particular appetite for hair is evident. The habit appears to be similar to other more or less innocuous habits as nail biting or masturbation which involve bodily manipulation.

As in the case described (Case 3) in this report the habit ordinarily functions in times of nervous stress or boredom. The patient, usually a girl, takes hold of her hair which is long enough to be brought down to the mouth, chews on it and swallows it. Occasionally a long hair is pulled out, twisted on the finger and swallowed.

The mechanism of formation of trichobezoar is not clearly understood. The lack of friction between the hair and the gastric mucosa may account for the inability of the individual hairs to be propelled along the stomach with peristalsis. Admixture with food permits some hairs to be passed. It was shown by Meilchen that hair fed to rabbits remained in the stomach. If, however, the hairs were mixed with dough, hair balls were found in the lower gastro-intestinal tract, but were not passed completely. If rats are given hair and food containing about 25 per cent fat, hair balls are found in the stomach. If dry food is given, however, no hair balls are found.

In the majority of cases the hair ball has been confined to the stomach, accumulates and assumes the shape of the stomach. Occasionally portions of the gastric mass may be extruded through the pylorus and passed down to become lodged in the small intestine, with the production of intestinal obstruction. This fact must be borne in mind in the surgical management of trichobezoar.

It is a curious fact that regardless of the hair color of the host trichobezoars are uniformly greenish-black in color. They are also exceedingly foul in odor. Unpleasant breath, however, was not noted to be characteristic of trichobezoar despite the invariable foulness of the mass. Apparently the cardiac orifice of the stomach is capable of retaining the odor within the organ.

The clinical manifestations of trichobezoar are usually slight. Despite the presence of a huge hairball filling the stomach the patient may only complain of vague post-prandial distress and mild epigastric pain. More pronounced symptoms, however, may occur. In the well advanced case the trichobezoar is readily palpable as a firm, somewhat movable epigastric mass conforming to the contour of the stomach. Crepitation, as observed in Case 3 is rarely elicited. The patient is likely to have a mild secondary anemia, and may show evidence of weight loss. The remainder of the examination is negative, except for the unusual instance where intestinal obstruction, gastric ulcer or perforation is the presenting symptom.

The diagnosis is usually made roentgenologically. X-ray examination of the abdomen may show an opaque mass in the epigastrium as can be seen in Figures 1 and 2. A swallow of barium gives rise to characteristic picture outlining the intragastric mass. Gastroscopy is rarely necessary to confirm the diagnosis.

The only treatment is surgical. The special cautions to be observed include the preoperative preparation with transfusion, lavage and chemotherapy, the careful walling of the peritoneal cavity at the time of gastrotomy and post-operative use of indwelling gastric drainage and adequate fluid therapy. Cases 2 and 3 illustrate this ideal type of management.

Where operation was not carried out in 33 cases, there were 24 deaths; in 124 cases operated upon, there were 6 deaths. In 17 cases, where intestinal obstruction occurred, 8 deaths resulted; in 15 cases gastric ulcer was observed with 8 deaths; there were 5 cases of gastric perforation with 5 deaths and a total of 6 cases of peritonitis with 6 deaths. All these complications were much more frequent both absolutely and relatively in patients with phytobezoars than with trichobezoars.

#### CASE REPORTS

*Case 1.<sup>1</sup> Gastric Trichobezoar with Multiple Small Intestinal Trichobezoars; Death due to Intestinal Obstruction.*

*History* (Adm. 383183). A 25 year old colored housewife was admitted to The Mount Sinai Hospital because of a large epigastric mass. One year before her first admission she had had an episode of epigastric pain not associated with vomiting. Ten days before admission increasingly severe epigastric pain relieved by ingestion of food had begun. Six days later vomiting occurred with continuation of the pain and complete obstipation.

*Examination.* The significant physical finding was a smooth, firm epigastric mass, conforming to the contour of the stomach. It was non-tender and freely movable vertically.

Flat plate examination of the stomach showed irregular mottling in the region of the stomach and a slightly distended loop of small bowel in the left upper quadrant.

*Operation.* A hair ball 16 x 6 x 5 cm. filling the stomach was removed. A mass was palpable in the upper jejunum. An enteroanastomosis both proximal and distal to this mass was performed with the removal of two more hair balls, one the size of a lima bean, the other 7 x 3 x 1.5 cm.

*Course.* Four weeks later the patient was readmitted with symptoms and signs of upper intestinal obstruction. At laparotomy an ileostomy was performed with the removal of another hairball 8 x 3 x 4 cm. lodged at the enteroanastomosis.

About three weeks later she was admitted for the third time after six days of upper intestinal obstruction. Her condition was desperate. An ileotomy was performed under local anesthesia and a fifth hairball 9 x 4 x 3.5 cm. was removed. The patient did not survive.

At post-mortem examination a sixth hairball was recovered.

*Case 2. Intragastric Trichobezoar—Successful Removal with Possibility of Recurrence.*

*History* (Adm. 487337). An 8 year old Jewish girl was admitted to the Pediatric Service chiefly because of the finding of an epigastric mass during a routine examination when the child was suffering with a sore throat. Two months before admission the patient had had mild right lower quadrant pain without nausea and vomiting and had been examined

<sup>1</sup> This case was observed at the time Dr. Richard Lewisohn was in charge of the Surgical Service.

by a physician because of the question of appendicitis. At that time an epigastric mass was noted. One week before admission the patient was noted to have poor appetite and occasional nausea and vomiting.

*Examination.* Psychiatric examination during her hospital stay disclosed that the child's mentality was lowest dull normal, so that she undoubtedly had difficulty keeping up with her classmates in school. She was the older of two children, her younger sister having died about one month previously. It was further revealed that enuresis had ceased only three years previously. At the age of six years she had had frequent screaming tantrums. She still sucked her thumb and bit her fingernails. She was said to have an aver-



FIG. 1

sion for hair anywhere near her food. While she had never been observed swallowing hair, she had been seen pulling her hair out. Hair was frequently found in her bed. This also occurred during her hospital stay and after discharge.

The girl was slightly obese. Her hair was shoulder length. The striking findings on physical examination was the presence of a large, firm, smooth sausage shaped mass, three inches in breadth, extending across the epigastrium, disappearing under each costal margin. It was non-tender and said to be slightly movable.

X-ray examination showed an intragastric mass which was mottled in appearance and suggested phyto bezoar to the examiner (fig. 1). On x-ray examination with barium, a

large filling defect occupying the entire stomach was demonstrated confirming the presence of a large foreign body (fig. 2).

*Operation.* The patient was prepared for operation with intravenous fluids and sulfathiazole by mouth, and transferred to the Surgical Service of Dr. Ralph Colp.

The abdomen was entered through a midline incision. The wound edges and peritoneal cavity were carefully packed off. The stomach was opened through a longitudinal incision, and the intact trichobezoar consisting of a mass of black hair matted together with greasy material and measuring 10 x 10 x 5 cm. was removed. The stomach was closed with a Connell inverting suture of catgut and reinforcing interrupted Lembert sutures of linen.



FIG. 2

Exploration revealed no further masses. Five grams of sulfanilamide were placed in the peritoneal cavity in proximity to the suture line of the stomach, and the abdomen was closed without drainage by means of through and through black silk sutures.

*Course.* Postoperatively constant gastric drainage was maintained by means of a Levin tube, and fluid balance was assured with intravenous 5 per cent glucose in saline. The sutures were removed on the thirteenth day, and the wound had healed *per primam*. When seen approximately four months later, the patient had gained ten pounds. She had received a short hair cut.

*Comment.* The difficulty which persists in this case is the possibility of recurrence, since hairs continue to be found in the patient's bed, and trichophagia while not observed, cannot be excluded. The psychic trauma of the operation may not be sufficient to put an end to this particular habit. The apparent emotional instability may have been affected only adversely by the operation.

*Case 3. Trichobezoar—Successful Removal.*

*History* (Adm. 492567). A 13 year old Jewish girl came under observation because of the presence of an epigastric mass. Two years before admission she had been noted to have a mysterious loss of hair from her scalp not due to any obvious dermatological or constitutional condition. There was poor nutrition and a ten day episode of epigastric pain with occasional vomiting. The patient remained malnourished, had a poor appetite, complaining of fullness after eating a small amount of food and had infrequent episodes of vomiting. The last attack of vomiting occurred six days before admission. Because of



FIG. 3

the finding of an abdominal mass, x-ray examination was made and surgical consultation sought.

The patient was the younger of two sisters. Her birth and development were normal, and she was said to be proficient in her school work, having recently skipped a grade. Her parents volunteered the information that she was a nervous, high-strung girl, but they had never noticed trichophagia. On direct questioning of the patient, the admission was obtained that in times of stress, as before examinations in school, she would twist her hair around her finger, pull it out, chew it and swallow it. She also admitted nail biting.

*Examination.* She was a thin, but well developed pubescent girl, with light brown, moderately long hair. Filling the epigastrium and extending to the right hypochondrium, there was an enormous, firm mass conforming to the outline of a dilated stomach and roughly sausage shaped, the right extremity extending into the right hypochondrium. Crepitation was obtainable on palpation of this mass. The remainder of the examination was normal including blood and urine studies.

*Operation.* Because of the malnourished state of the patient she was prepared for operation by means of a transfusion and intravenous 5 per cent glucose in saline. Sulfathiazole also was given preoperatively.

At operation, a midline incision was made, the wound edges walled off, and the stomach delivered. The peritoneal cavity was carefully packed off. The stomach was opened by

means of a longitudinal incision, and a hair ball 36 x 20 x 10 cm. weighing 1075 grams was removed intact (fig. 3). The muscularis of the stomach was noted to be hypertrophied. The stomach was then closed by means of inner Connell running suture of catgut and outer interrupted Lembert sutures of linen. Exploration of the gastro-intestinal tract and of the peritoneal cavity revealed no abnormality. The abdomen was closed with through-and-through black silk sutures.

*Course.* Postoperatively the patient received intravenous fluid and constant gastric drainage by means of a Levin tube. Convalescence was uneventful. The patient was discharged on the sixth postoperative day, the wound having healed by primary union.

Sixty days later, the patient had gained 30 pounds.

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# INTUSSUSCEPTION DUE TO MECKEL'S DIVERTICULUM

## RECOVERY FOLLOWING RESECTION AND ILEO-TRANSVERSE COLOSTOMY

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[From the Surgical Service of Dr. Ralph Colp]

Intussusception of the small intestine due to Meckel's diverticulum is not common. In a careful survey of the literature, Harkins in 1933 was able to find reports of 160 instances of this condition. Since that time about three or four cases can be found annually in the Cumulative Index Medicus. We have been fortunate to encounter an example of ileo-ileal intussusception due to a Meckel's diverticulum which was treated by resection and ileo-transverse colostomy. The rarity of this condition and the successful outcome in our patient merit publication and review of some interesting features of this pathologic and clinical entity.

### CASE REPORT

*History.* (Adm. 494855): A white boy, aged 14 years, was admitted to the Hospital on September 7, 1942. His present illness consisted of intermittent, cramp-like upper abdominal pain which began three days previously and continued to the time of admission. Forty-eight hours after the onset of pain he began to have frequent loose bowel movements which were normal in color and failed to contain either blood, mucus or pus. These symptoms were soon followed by nausea and vomiting. His previous health had been excellent except for pneumonia at the age of seven years. There had never been any previous gastro-intestinal symptoms.

*Examination:* The boy appeared fairly comfortable and not acutely ill. Temperature was 100.6°F. His heart and lungs were normal; pulse 64 and respirations 20 per minute; the blood pressure was 130 systolic and 84 diastolic. The abdomen was not distended and was soft throughout. On more careful palpation, a soft, slightly tender, almost cystic mass the size of a baseball was felt to the right of the umbilicus. This mass seemed very freely movable in all directions. Rectal examination failed to reveal any abnormality and there was no evidence of blood on the examining finger.

*Laboratory Data:* Blood: hemoglobin, 94 per cent; white blood count, 9,450 with 74 per cent polymorphonuclear leucocytes; 21 per cent lymphocytes; 5 per cent monocytes. Urine: normal.

*Course:* The various clinical diagnoses made were mesenteric cyst; regional ileitis; perforated Meckel's diverticulum with abscess. This last diagnosis was suggested by the resident surgeon Dr. E. Hurwitt. It seemed obvious that exploratory laparotomy was indicated.

*Operation:* With the patient under ethylene and ether anesthesia, the mass which previously was felt to the right of the umbilicus was now palpable in the left upper abdomen. Despite this, a right para-umbilical muscle splitting incision was made and the abdomen was opened. No free fluid was present. When the mass was delivered it proved to be an intussusception of the ileum. The intussusception was about 16 inches long involving not only the ileum but also part of the mesentery. It was about 5 cm. in diameter and markedly congested. The head of the intussusceptum was felt about 10 cm. from the ileocecal junction. The proximal ileum was moderately distended and edematous while the distal ileum was collapsed and normal in color. An attempt was made to reduce the intussusception but this was not successful. It seemed that more strenuous efforts at reduction

would result in a rupture of the distended and edematous intestine. Accordingly, an aseptic resection of the diseased bowel was carried out between Payr clamps. Because the distal stump of ileum was only 7 cm. in length, an ileo-transverse colostomy was done. Five grams of sulfanilamide were placed into the peritoneal cavity and the abdomen was closed in layers without drainage.

*Postoperative Course:* Fluids were administered intravenously for forty-eight hours. The patient's temperature rose to 103°F. twenty-four hours after operation and gradually subsided to normal. His bowels moved first on the third postoperative day and he had several daily bowel movements until his discharge from the hospital on the thirteenth day after operation. The wound healed by primary union.

*Surgical Pathology:* An attempt to reduce the specimen caused it to rupture. It consisted of 71 cm. of ileum with a Meckel's diverticulum. Six centimeters from one end of the resected specimen showed a Meckel's diverticulum 6.5 cm. in length and 3 cm. in width. The distal part of the diverticulum was thick, dark and red. The ileum for 35 cm. showed varying degrees of congestion and for 10 cm. appeared necrotic. Microscopic diagnosis was "portion of ileum and Meckel's diverticulum with gastric mucosa showing hemorrhagic infarction."

#### DISCUSSION

This subject was admirably studied and reviewed by Harkins in 1933 on the basis of 160 cases collected from the literature. Many interesting features were disclosed. The earliest known specimen of intussusception due to a Meckel's diverticulum is dated 1842 in the Anatomical Museum of St. Bartholomew's Hospital. The incidence of Meckel's diverticulum among normal people has been variously estimated. On the basis of necropsies, Turner found 0.8 per cent; Forgue and Riche 1.4 per cent; Cunningham 2.2 per cent. Harkins found an incidence of 1.3 per cent in reports of 25,149 necropsies. The proportion of all cases of intussusception caused by Meckel's diverticulum have been reported by Fitzwilliams, 15 in 1000 cases of intussusception; Eliot and Corscaden, 29 in 300; Koch and Oerum, 7 in 400. This makes an average of 1.5 per cent of all cases of intussusception. It is also stated that when Meckel's diverticulum gives rise to trouble, in 17 per cent the difficulty is due to intussusception. Halstead calculated that 6 per cent of 991 cases of acute intestinal obstruction were caused by a Meckel's diverticulum. Although 60 per cent of all cases of intussusception due to all causes occur under 1 year of age, the average age for those due to Meckel's diverticulum is 13 years. Only 6 patients in Harkins' series of 160 cases were under 1 year of age. It is of interest to note that a tumor was present at the tip of a Meckel's diverticulum in 26 out of 114 cases.

Although one can theorize as to the manner in which an intussusception is caused by a Meckel's diverticulum, the diverticulum forms the focal point which causes the bowel to invaginate and is most frequently near the head of the intussusceptum. It acts in the same manner as a tumor of the bowel in initiating the invagination. Despite the fact that the small bowel is involved, the obstruction is not usually complete and the symptoms may go on for several days before medical attention is sought. As with other types of intussusceptions, this type can slough and pass out of the rectum spontaneously. The presence of a distended Meckel's diverticulum makes reduction more difficult in this

group of intussusceptions. The mortality in general for intussusception due to Meckel's diverticulum is 56 per cent in patients under 5 years and 35 per cent in those over 5 years of age.

A summary of the clinical features as given by Harkins follows: Average age in 113 cases, 13 years; sex in 105 cases, 83 males and 22 females; abdominal pain present in 97 out of 98 cases; previous abdominal crises in two-thirds of the cases where data was given; vomiting present, 82 cases; tumor in right lower abdomen, 50 per cent of cases; average duration of symptoms, 81 hours in 88 cases; tumor in diverticulum present, 26 cases; resection of bowel necessary in 61 out of 114 cases.

#### SUMMARY

1. A case of ileo-ileal intussusception due to a Meckel's diverticulum is reported. Recovery followed resection of the intussusception with ileo-transverse colostomy.

2. Some interesting features of this clinico-pathologic condition are reviewed.

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## UREMIA FOLLOWING INHALATION OF CARBON TETRACHLORIDE

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It is common knowledge that carbon tetrachloride causes liver necrosis. However, the clinical picture of poisoning by this chemical can be dominated by renal damage, even to the almost complete absence of signs or symptoms of hepatic involvement. Such cases may present difficulty in diagnosis if the history of exposure is lacking or if such a history is disregarded. Such clinical reports have been repeatedly described in recent years (1, 2, 3, 4) and excellently reviewed by Smetana (5). It is the purpose of this communication to report another case, one in which the diagnosis was delayed because of lack of familiarity with the syndrome.

Poisoning by carbon tetrachloride may occur through inhalation or ingestion. The vapor is most often encountered through its widespread use as a dry cleaning agent, but the chemical is also found in portable fire extinguishers (1) and is sometimes used as a solvent for paint (3). Brief exposure to fumes may damage the kidneys severely. One instance of fatal uremia has been described following a single exposure of about four hours (2), and another of advanced azotemia after the use of a portable fire extinguisher in a small room for only five minutes (1).

Poisoning may occur by the oral route when the drug is given as a vermifuge or when it is drunk by mistake or for suicidal purposes. In these cases hepatic damage is most severe, but in poisoning by inhalation the renal damage dominates the clinical picture (5). In two fatal cases Smetana found the renal disease similar to that found in mercuric chloride poisoning, except for the absence of tubular calcification. He also found doubly refracting tubular concretions of unknown nature.

The clinical diagnosis of renal damage due to carbon tetrachloride may be made by the history of exposure, followed by persistent vomiting and oliguria, and the development of uremia with or without hypertension and edema. The findings in the urine are not specific, consisting of albuminuria with red and white blood cells in the sediment. These findings may be minimal or may reach the proportions of gross hematuria. Physical examination and blood chemistry determinations will almost always implicate the liver to some degree, be it only tenderness in the right upper quadrant or subclinical icterus (2, 3, 4, 5).

### CASE REPORT

*History.* (Adm. 498523) A Puerto Rican woman, 22 years of age, entered the hospital complaining of vomiting of ten days duration. The history, as obtained at the time of admission, was fragmentary, because of language difficulty and the prostrating acute illness of the patient. She stated, however, that she worked in a factory where costume jewelry was made; that she had begun to vomit about ten days before admission, and attributed

her illness to fumes which she had inhaled during the course of her work. Several co-workers had also vomited but had recovered quickly. She continued to vomit subsequently, and was unable to retain either food or drink. A few days before admission she noticed a skin eruption.

*Examination.* The patient appeared acutely ill and retched frequently. Her breath was foul and suggestive of uremia. The skin showed an eruption chiefly localized to the extensor surfaces. It consisted of dark red and purplish-red macules, papules and large patches of a hemorrhagic character. There was tenderness in the right upper quadrant, although the liver was not distinctly felt. The blood pressure was 105 systolic and 60 diastolic. There was no edema. The fundi were normal.

TABLE I

DATE	FLUID		URINE SP. GR.	BLOOD						MISCELLANEOUS
	Intake	Output		Urea	CO <sub>2</sub>	Chlor.	Ict. Ind.	Cholest.	Ester	
11-29			1010							
11-30	2530		1014	169	50.8	375	2			Sugar, 115
12-1	1900	800		170	61.2	400				
12-2	2420	510		120	57.8	435				Calcium, 6, phosphorus, 9
-3	2750	1600	1010	119	54.4	435				
-4	2475	2060								
-5	1480	1675	1004	113	52.4	490				Albumin, 4.2, globulin, 18
-6	3745	2075								
-7	2110	2050	1008-11	80	50.7	585		180		
-8	2470	2080	1008-10							
-9	I.V.		1010	48						
-10	Stopped		1012							P.S.P., 35%
-14				29						Cephalin flocculation, neg.
-16			1012	24			2	240	180	
-17			1008-14	(concentration test)						Calcium, 10.4, phos. 4.5
-18			1016					260	185	Prothrombin time, 93%
-19			1002							Galactose tolerance test, less than 0.5 gm.
-21			1012	24						P.S.P., 100%
-22			1010							
-24			1010-12	(concentration test)						

*Laboratory Data.* Blood: hemoglobin, 70 per cent; white blood cells 17,450, with 78 per cent segmented polymorphonuclear leucocytes, 6 per cent non-segmented forms, 6 per cent lymphocytes, 6 per cent monocytes and 4 per cent eosinophiles. Blood urea nitrogen, 169 mg. per cent; blood chlorides (as sodium chloride), 375 mg. per cent; blood sugar, 115 mg. per cent; carbon dioxide content, 50.8 volumes per cent; and blood icterus index, 2 (see Table I). Blood Wassermann reaction, negative. Urine: alkaline in reaction; specific gravity, 1014; urinary protein, 1 plus; glucose and acetone, absent; bile, negative; urobilinogen, 1:2. In a catheterized specimen the sediment showed 3-4 red blood cells per high power field, many white blood cells, with occasional clumps, and many granular casts. Urine culture yielded staphylococcus albus B. The stool was dark brown, liquid, and negative to guaiac.

*Course.* As the blood chemistry determinations were not available until two days after admission, and the severity of the azotemia not realized, the diagnosis was not clear. The

patient was nevertheless treated with intravenous glucose in saline. Vomiting stopped after two days, and the urinary output, which was poor at first, gradually rose. Hypertension did not occur. The rash faded within a few days.

Meanwhile the patient's place of employment had been investigated by the New York State Department of Labor, and through the efforts of Dr. Adelaide Ross Smith of the Division of Industrial Hygiene,<sup>1</sup> it was ascertained that the patient had probably been exposed to carbon tetrachloride fumes. The following additional facts were then obtained. The patient worked in a room with several other women, dipping beads into colored paints. At the same table white beads were dipped into carbon tetrachloride solution to clean them. Apparently acetone had ordinarily been used for this purpose. The patient had only worked in the plant for one week. The day in question was cold and rainy, and the windows were closed. The fumes from the dipping pans were more noticeable than usual. The patient felt dizzy in the afternoon and vomited, but returned to her work. Vomiting recurred several times, and she was eventually forced to leave the plant. At least three other girls were stricken with vomiting, but apparently returned to work the next day. After returning home the patient continued to vomit and noted marked oliguria. As catamenia was present, hematuria would not have been noticed. Some difficulty in vision occurred on about the fifth day, and the rash appeared three days before admission.

As the nature of the toxic agent was not known until twenty-six days after onset of the illness, no concerted effort to estimate liver function was made until then. At that time no evidence of liver damage was found (see Table I).

The subsequent course was uneventful and the patient was discharged, symptom free, after one month of hospitalization. At this time, the only remaining evidence of renal damage was persistence of fixation of specific gravity. The urine showed a very faint trace of albumin and a few white blood cells.

One month later the patient was seen again. The blood urea nitrogen was normal, the blood pressure was normal, and a urine concentration test showed the maximum specific gravity to be 1022. The urine contained no albumin, and only a few white blood cells on microscopic examination. The patient had apparently recovered completely.

#### COMMENT

The only indication of liver involvement in this case was tenderness in the right upper quadrant at the time of admission—the significance of which was not appreciated at the time. Nevertheless, it is possible that considerable liver damage occurred. It is only necessary to cite the experience of Ashe and Sailer (2) who reported a case of fatal uremia, in which a blood icterus index of 11 on the fifteenth day after exposure was the only evidence of hepatic damage, nevertheless at post-mortem examination the liver showed marked central necrosis.

A skin eruption, which was present in this patient, is apparently an uncommon finding, although it has been reported in at least one previous case (6).

In this, as in other instances (1, 5) other persons besides the patient were equally exposed to the fumes, but developed few and transient symptoms, indicating a distinct variation in susceptibility.

Finally, the extremely low blood chloride level and the severe and persistent vomiting raised the question as to the role played by pre-renal deviation of fluid in the pathogenesis of the azotemia. Certainly the vomiting in poisoning by

<sup>1</sup> This case will be reported by Dr. Smith in an article to appear in the "Industrial Bulletin," in which the industrial hazards relative to the halogenated hydrocarbons will be stressed.

inhalation of carbon tetrachloride occurs much too soon (2, 3) to be a manifestation of uremia. Furthermore, low levels of blood chloride have been noted previously (2) and cannot be explained on the basis of renal insufficiency alone, in the absence of acidosis. The presence of low urinary specific gravity so late in the course of the disease does not exclude pre-renal azotemia (7), although the persistence of hyposthenuria indicates considerable renal damage. The striking improvement following intravenous administration of glucose in saline solution, on the other hand, demonstrates that the renal damage was reversible.

#### SUMMARY

A non-fatal case of uremia is reported, which followed occupational exposure to carbon tetrachloride vapor. The only evidence of liver damage was tenderness over the right upper quadrant. Vomiting was the most striking symptom and probably contributed to the azotemia.

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## ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

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### CHAPTER 3

#### THE BIOLOGY OF ACHLORHYDRIA IN RELATION TO ANEMIA

The term "achlorhydria" represents an absence of hydrochloric acid in the stomach while "achylia gastrica" implies in addition the absence of pepsin. For clinical purposes this distinction is of insignificant importance.<sup>2</sup> There is probably no congenital achlorhydria. In 55 newborn unfed infants, Hess (1) found as much as 10 cc. stomach contents with acidities of normal range. Hawksley, Lightwood and Bailey (2) found hydrochloric acid in all healthy infants after the fourth week of life. However, it is generally agreed that the incidence of achlorhydria increases with age (Conner (3), Bockus, Bank and Willard (4)), so that by the seventh decade the incidence is close to 30 per cent. In those suffering from gastric complaints, Conner (3) found an average of 15.2 per cent. The general average in health varies with the method used. Bockus, Bank and Willard (4) using histamine and a two hour method found an average of 5.7 per cent. Winkelstein's (5) percentage using both histamine and neutral red was 2.2 per cent and when he excluded cases of pernicious anemia, carcinoma, gall bladder disease and Graves' syndrome, the average was 1.2 per cent which represents what he terms "essential" achlorhydria.

There is a remarkable familial and hereditary tendency to acquire achlorhydria. This was disclosed in the study of the incidence of achlorhydria in blood relatives of patients who suffered from pernicious anemia. Thus Conner (3) found that the incidence including all decades was 25.9 per cent and that there was a progressive incidence with age, so that by the seventh decade the incidence was 57.1 per cent. In not a single incidence did achlorhydria occur before the age of 10 years. Wilkinson and Brockbank's (6) figures are practically identical with those of Conner, 24.1 per cent. Whether this tendency follows the Mendelian law and whether it is dominant or recessive, can only be determined by observations on families in whom the disease occurs in three or more generations, and inasmuch as pernicious anemia usually develops only in middle age, such observations would require a long period of follow-up. The significance of these data in relation to pernicious anemia will be discussed later.

In all likelihood, the development of achlorhydria is not sudden but gradual.

<sup>1</sup> This is the third chapter in a series of essays by Dr. Eli Moschcowitz in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend towards rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed in a monograph.—Ed.

<sup>2</sup> In this discussion we shall refer only to true achlorhydrias, i.e., where no hydrochloric acid is found after stimulation with histamine.

Bockus, Bank and Willard (4) noted the gradual decrease in acid to disappearance in a few of their patients.

Martius, many years ago, regarded the achlorhydria as primary and constitutional, but, largely sponsored by Faber (7), and since encouraged by gastroscopists, most current writers ascribe the achlorhydria as secondary to a "chronic atrophic gastritis." Faber found extensive round cell infiltration, with progressive atrophy of the mucosa, fibrosis, cystic dilatation of the gastric glands and a metaplastic conversion of portions of the mucosa to the intestinal type. Brown (8) found in 37 of 42 cases of pernicious anemia a disappearance of the acidophilic cells and in 41, a chronic gastritis similar to that described by Faber. In 20 of the cases which had received therapy, the histologic picture was unchanged. In eight autopsies on patients with pernicious anemia, Meulengracht (9) found a gastritis in the fundus of the stomach with disappearance of the acid and chief cells, but little or no change in the pylorus. He found difficulty in reconciling these findings with his previous observation (9) that in pigs the antianemic or intrinsic factor is found in the pylorus and neighboring duodenum (pyloric gland). This discrepancy has since been solved by Fox and Castle (10) who while confirming Meulengracht's work on the stomach of the pig have found that in the human being the fundus and cardia and not the pylorus contain most sites for the formation of the intrinsic factor. The work of Fox and Castle also serves as the explanation for the rarity of pernicious anemia after resections of the stomach, even when only a small portion of the fundus is left *in situ*. On the other hand, Magnus and Ungley (11) found no evidence of a gastritis in pernicious anemia, but an atrophy of all the coats of the stomach. The mucosa was represented by a surface epithelium with a few scattered glands lined by mucus producing cells, while the oxyntic and peptic cells disappeared. In several stomachs they also found areas of metaplastic intestinal epithelium. There was no involvement of the pyloric region or of Brunner's glands.

Any discussion of the relation of atrophic gastritis to achlorhydria with or without pernicious anemia is inevitably linked up with the relation of gastritis, whether atrophic or hypertrophic, to other diseases. It seems that there has been an uncritical acceptance of these morphologic changes as indicative of diseased gastric states without taking into consideration whether these changes may be the result of the normal involution of age. Hamperl (12) and Hillenbrand (13) found a high incidence of chronic gastritis in patients in later life who were free from gastric complaints. Hebbel (14) in autopsy material on similar individuals found hypertrophic gastritis of any degree rare below the age of thirty, and severe changes uncommon after the fiftieth year, while atrophic gastritis was exhibited in 30 per cent of 108 cases past the age of fifty. Benedict and Mallory (15) regard the hypertrophic gastritis as an exaggeration of the physiologic plasma cells and lymphocytic infiltration of the normal stomach.

Gastroscopy has not helped in the solution of the problem because there has been insufficient correlation with histology. In the few studies that have been thus far reported, there has been only an approximate confirmation. Thus Swalm and Morrison (16) report that gastroscopy only corroborates the clinical

findings in 52 per cent of their cases, while on the other hand, chronic gastritis may be present with a normal gastroscopic picture. In 25 per cent of their cases the gastroscopic appearance of a mild, moderate or chronic gastritis was contradicted by the histologic examination. Benedict and Mallory (15) in a study of resected stomachs showed complete agreement between the gastroscopic and histologic findings in 54.9 per cent and partial agreement in 33 per cent. There was no correlation in 11.8 per cent. The pathologist and the gastroscopist were fairly well agreed in the diagnosis of atrophy. Further unbiased studies on such correlations are much to be desired.

The concept of chronic atrophic gastritis as the cause of achlorhydria is confronted with some irreconcilable clinical facts concerning achlorhydria and pernicious anemia. Aside from the undefined nature of the lesion as an inflammation, according to accepted criteria, this concept does not explain the following observations: 1) The comparative absence of achlorhydria and pernicious anemia before puberty; 2) their familial and hereditary character; 3) the restoration of the gastroscopic picture of atrophic gastritis to normal after specific therapy was instituted (Schindler, Kirsner and Palmer (18)). Whether this gastroscopic transformation is only one of appearance or represents a histologic restitution is only answerable by a before and after biopsy. To complicate matters, Schindler and his co-workers (18) found that in 5 per cent of patients with complete anacidity proven by histamine the mucosa of the stomach was gastroscopically normal. 4) The occasional gastroscopic picture of hypertrophic gastritis in achlorhydria (Winkelstein (5) 2 out of 14 cases). The fact that no assignable cause for the development of the atrophic gastritis can be ascribed is in favor of the primary nature of the achlorhydria. The problem as to whether the achlorhydria is primary or secondary may be solved by studying the histology of the stomach in patients in whom a complete achlorhydria has been attained, for instance, by partial gastrectomy. Thus far, such a study has, as far as I am aware, not been pursued.

*A. Relation of achlorhydria to idiopathic hypochromic anemia.* Idiopathic hypochromic anemia is a syndrome that affects mostly women of middle age and is characterized by weakness, pallor, atrophy of the tongue, brittle finger nails and an enlarged spleen. The anemia is not attended by any evidences of hemolysis. The Plummer-Vinson syndrome is an occasional accompaniment. These patients respond promptly to the administration of iron but not to liver. Nearly all possess a complete achlorhydria as attested by histamine. Wintrobe and Beebe (20) determined this in all of 12 patients. Castle and Minot (21) found achlorhydria in 25 out of 30 individuals, Damashek (22) in 14 out of 17. Castle, Townsend, and Heath (23) found the intrinsic factor invariably present in hypochromic anemia. This is of special significance in view of what we shall soon discuss, namely, the occasional transition of idiopathic hypochromic anemia into true pernicious anemia.

The gastroscopic picture of atrophic gastritis has been reported in hypochromic anemia. In one case reported by Schindler, Kirsner and Palmer (18), the gastroscopic picture was restored to normal by iron. Schiff and Goodman (24) report a similar observation.

The prevailing view of the pathogenesis of hypochromic anemia is based on the observations of Mettier and Minot (25) who showed that in idiopathic hypochromic anemia, the response of the bone marrow to iron is greater when the contents of the upper intestinal tract are slightly acid than when it is alkaline. Minot and Castle (21) in addition, suggest that the widespread changes in the intestinal tract as reflected in the glossitis, may interfere with the absorption of iron and they cite the observation of Singer and Wechsler (26) who found inadequate absorption of galactose in achylic states. Its preponderance in women is ascribed to the loss of blood during menstruation which acts as a conditioning factor. Other losses of blood, for instance from hemorrhoids (Bloomfield (27)) may act in a similar manner.

The probability is strong that hypochromic anemia is not a disease, because it has altogether too many backgrounds. It may be associated with sprue, pregnancy, myxedema and may arise after gastroenterostomy or partial gastrectomy. Bloomfield (27) holds that hypochromic anemia and chlorosis have so many clinical features in common as to be indistinguishable.

B. *The relation of achlorhydria to pernicious anemia.* That an achlorhydria is an almost ever present association in pernicious anemia is acknowledged except in rare instances (Castle, Heath and Strauss (28)). It is now well accepted that the achlorhydria antedates the onset of the anemia, sometimes by many years (for references see Moschcowitz (29)). Moreover, the achlorhydria never returns despite restoration of the blood picture by specific therapy. There is ample testimony that pernicious anemia is often familial and hereditary (Moschcowitz (29)), sometimes occurring in three generations, and this is reflected in the frequency in which achlorhydria is found in blood relatives of individuals affected by pernicious anemia (Conner (3), Wilkinson and Brockbank (6)). It is evident therefore that achlorhydria is a significant conditioning factor for the production of pernicious anemia and this is confirmed by the reports of pernicious anemia that occasionally follow complete gastrectomy (Finney and Rienhoff (30)). However, the causative relation between achlorhydria and pernicious anemia is not absolute because achlorhydria may be persistent for as much as seven years without the development of pernicious anemia (Bloomfield and Pollard (32)) and pernicious anemia may develop in an individual with hydrochloric acid in the stomach. The problem was largely clarified by the classic work of Castle who showed that in pernicious anemia there was an absence of an intrinsic factor. The intrinsic factor is not pepsin, although the two are in a measure associated (Davies (33)). The absence of an intrinsic factor in pernicious anemia seems constant, because as Castle, Heath and Strauss (28) have shown, it was absent in pernicious anemia with normal gastric juices and in achylic individuals without an anemia or with hypochromic anemia.

C. *The transition of idiopathic hypochromic anemia to pernicious anemia.* The common association of some of the clinical phenomena in both conditions, notably the anemia, the atrophy of the tongue and the achlorhydria would suggest that the two are related and such indeed is the case, for there are ever increasing reports of the transition of idiopathic hypochromic anemia to pernicious anemia

(Castle and Minot (21), Witts (34), Davies (33), Heath (35), Gram (36), Damashek and Miller (37)). Apparently the transition is not sudden because all of these observers report cases where clinical features of both are combined, for instance, pernicious anemia with a low color index, subacute combined degeneration of the spinal cord with a hyperchromic anemia (Witts (34)). In this category may be classified the cases of pernicious anemia who require iron to maintain a normal blood level (Beebe and Lewis (38), Heath (35)). In all likelihood, this transition is more common than the reported cases indicate and it is by no means improbable that many patients with pernicious anemia pass through a hypochromic stage, but this phase is hidden from us because the patient is not examined until the blood picture is full blown. This transition also accounts for the not infrequent reports of a familial idiopathic hypochromic anemia in the blood relatives of patients with pernicious anemia (Davies (33), Damashek (22), Heath (35), Witts (34), Conner (3), Mustelin (39), Patek (40), Gram (36)). Faber and Gram (41) describe a family of three generations in whom most of the members were afflicted with either pernicious or idiopathic microcytic anemia.

It seems remarkable that these two conditions that are biologically identical should respond entirely differently to the two specific remedies, liver and iron, even though there are borderline cases in which both are effective when given simultaneously. The precise mechanism is not known. Hurst (42) speculates that the atrophic process begins in the proximal half of the stomach when acid is excreted and later involves the pylorus and duodenum. Inasmuch as the intrinsic factor of Castle has thus far never been found in pernicious anemia and always in hypochromic anemia (Castle, Townsend and Heath (43), Hartfall (44)), it is reasonable to infer that the transition is due to the disappearance of this factor. The spontaneous biologic course is always in the direction of hypochromic to pernicious anemia and not reversely.

D. *Relation of achlorhydria to the anemia of pregnancy.* The work of Strauss and Castle (45), has clarified considerably our knowledge. In 24 pregnant women, they showed that 75 per cent did not secrete the normal amount of hydrochloric acid during more than half the period of pregnancy. Three patients had achlorhydria which did not return after delivery. After delivery the average secretion was three times as great.

Hypochromic anemia in pregnancy occurs during the last trimester and is ascribed to the demands of the growing fetus, plus dietary insufficiency and is especially conditioned by achlorhydria or hypoacidity, or a related gastrointestinal disturbance. This form of anemia is usually relieved by iron. Occasionally, the anemia of pregnancy is macrocytic; this occurred in 6 out of 36 pregnant women with anemia, and in all the intrinsic factor was lacking. But the macrocytic anemia of pregnancy differs from pernicious anemia in that there may be no relapse after recovery, although liver is not administered; and furthermore, achlorhydria was only found in two of the six cases. In one, the acid returned two years later. Strauss and Castle suggest that in the macrocytic anemia of pregnancy there may be a combined deficiency of liver and iron, as proven by one of their cases. They also suggest that in the macrocytic anemia,

as in true pernicious anemia, there is a lack of both the intrinsic and extrinsic factors. In other words, in the anemias of pregnancy, similar mechanisms are at play as in idiopathic hypochromic anemia and in pernicious anemia. While the majority of pregnant women with macrocytic hypochromic anemia are cured after parturition, some require persistent treatment with specific measures. These represent accidental associations of pregnancy and pernicious anemia.

E. *The relation of achlorhydria to the anemia or sprue.* Tropical and non-tropical sprue have so many clinical characters in common that for our purpose they may be discussed together. In tropical sprue, Castle and Rhoads (46) found achlorhydria as tested by histamine in 30 per cent; in non-tropical sprue (Snell (47)) found achlorhydria in about 35 per cent (in six of the eight cases tested by histamine). Whether the hypoacidity that is so common in sprue, especially in the early stages, is evidence of a tendency to achlorhydria is unknown. In both tropical and non-tropical sprue both a hypochromic and a macrocytic hyperchromic anemia occur. In 22 cases of non-tropical sprue Snell found a hypochromic anemia in 5 and a macrocytic hyperchromic anemia in 17. Castle and his co-workers (48) regard the mechanism of the development of the macrocytic anemia in sprue as analogous to that of pernicious anemia. In other words, there is a failure in reaction between the extrinsic factor associated in many instances with vitamin B<sub>12</sub> (G) and an intrinsic factor. In addition, there is difficulty in absorption of substances from the intestinal tract resulting from this failure in the hematopoietic reaction. In one patient who died of sprue and macrocytic anemia, the liver contained no detectable hematopoietic principal. Thus the macrocytic anemia of sprue arises from the variable participation of three defects, the extrinsic factor, the intrinsic factor and absorption. Also as in pernicious anemia, the administration of liver, especially parenterally, is usually effective and in certain instances, as in pernicious anemia, iron must be added. The parallelism was further maintained by the experimental production in swine of a disease akin to sprue by feeding a modified canine black tongue diet (Miller and Rhoads (49)). They obtained a symptom complex marked by oral manifestations, achlorhydria and an anemia which is usually macrocytic but may be microcytic. The disease is associated with a loss of the intrinsic factor both in the stomach and in the liver. The achlorhydria preceded the anemia in every instance. The disease responds to liver extract but not to iron alone. The one important difference is the return of the hydrochloric acid in the experimental animals.

F. *The relation of achlorhydria to the anemia of myxedema.* The usual anemia that is associated with myxedema is normocytic or microcytic responding to thyroid, but a number of observers have reported a hyperchromic macrocytic type resembling that of pernicious anemia which requires the administration of liver in addition to thyroid (Means, Lerman and Castle (50) (5 cases), Davis (51) (1 case), Hölböhl (52) (3 cases), Lisser (53) (1 case)). In Means, Lerman and Castle's cases, the pernicious anemia preceded the development of the myxedema in three instances, followed the myxedema in one, and in the other the sequence could not be determined. All these observers report an associated achlorhydria.

Lerman and Means (54) found an achlorhydria in 53 per cent of their cases of myxedema. Golding (55) found the gastroscopic picture of mucosal atrophy in 10 of 11 cases, in one confirmed by histology. The lowered metabolic rate is especially significant because, as a rule, the rate in pernicious anemia is in the upper limits of normal (Myers and Dubois (56)). It is hardly likely that the association of pernicious anemia and myxedema is accidental in view of the comparative high incidence.

G. *The relation of achlorhydria to the anemia of gastric carcinoma.* The only significant relation we need discuss is that of pernicious anemia. The problem centers around three possibilities: 1) whether pernicious anemia with its achlorhydria acts as the soil upon which the carcinoma is engrafted (Hurst (57)); 2) whether the pernicious anemia results because of the achlorhydria engendered by the cancer; and 3) whether both diseases are accidentally associated. Doehring and Eusterman (58) report from the Mayo Clinic 40 cases of pernicious anemia associated with gastric carcinoma out of 1,014 cases of pernicious anemia admitted between the years 1935-1939 which is an incidence of 1.7 per cent, slightly higher than the incidence of gastric carcinoma in the general population. They very reasonably discuss the possibility that the age incidence of pernicious anemia has been prolonged in recent years through specific therapy which accounts for the increasing frequency with which this association has been noted in the Mayo Clinic. In 26 of the 40 cases the pernicious anemia clinically preceded the cancer, in 12 it was simultaneous and in 2 the carcinoma preceded the pernicious anemia. These sequences do not decide much because of the notorious dormant nature of both maladies. The fact that the anemia so often responds to liver treatment also does not help in the solution.

There is no reason to believe that every achlorhydria leads to either anemia or other disease. Bloomfield and Pollard (32) have followed over periods of one to seven years the fate of 45 patients in whom achlorhydria was found casually and in not a single one did any form of anemia or gastric carcinoma develop. Aside from the fact that even seven years is not a sufficient period of observation, it must be remembered that the development of the anemia is conditioned by other factors, notably, menstruation, loss of blood, intestinal absorption and above all, deficiency in the extrinsic substance. Only a far enough future with strict observation can decide this aspect of the problem.

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## CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, October 23, 1940*

Abdominal Hodgkin's Disease. No Superficial Lymph Node Enlargement.  
Macrocytic Anemia Resistant to Liver Therapy

*[Private Service of Drs. N. Rosenthal and A. Schiffrin]*

*History* (Adm. 462033; P.M.11605). A 68 year old white woman had complained of weakness and fatigability during the two years prior to her admission to the hospital, but otherwise was apparently in good health until the onset of the present illness. Three and a half months before she was admitted to the hospital she noticed a painless, cherry-sized lump in the right side of the neck. Ultra-violet irradiation was given by her family physician; the mass disappeared in approximately two weeks. Three months before admission she was seen by another physician because of increased fatigue. It was then noticed that she had become pale, was not eating as well as formerly, and she was found to have a temperature of 103.4°F.

She was hospitalized in another institution. During the three weeks' stay there, no definite diagnosis could be established. Examination at that time was said to be essentially negative except for pallor, evidence of recent weight loss, and fever which ranged from 101° to 104°F. Blood counts showed a moderate hypochromic anemia; hemoglobin 55 per cent, red blood cells 3,400,000. The white blood count varied from 6,000 to 8,000; no abnormal white blood cells were seen. Agglutination reactions against *B. melitensis*, typhoid and paratyphoid were negative. Because of anorexia and the absence of free hydrochloric acid in the gastric contents, the presence of a neoplasm in the gastro-intestinal tract was suspected, but no evidence to support this impression was obtained on roentgen examination. Cholecystogram revealed the presence of many stones in the gall-bladder. The development of glossitis and slight leucopenia, together with the appearance of a number of macrocytes in the blood, made the diagnosis of pernicious anemia seem more probable and liver therapy was instituted. This, however, was soon abandoned because of the appearance of tender swellings at the sites of the injections. Following repeated blood transfusions her general condition improved and the fever subsided. During a three weeks' stay at a convalescent home there was further improvement. However, the fever soon recurred, weakness increased, and her general condition again declined. She was therefore admitted to this hospital.

*Examination.* The patient was an extremely ill, weak, old woman, who was rather unresponsive. The temperature was 102.4°F. The skin was pale and yellow in color, the sclerae were icteric. The tongue was dry and red. No enlarged lymph nodes were palpable. Over the left lung base, the percussion note was impaired, and a few moist rales were heard over both lung bases. The cardiac findings were not noteworthy except for the

presence of a systolic murmur over the apical region. The rate was 93 per minute; the blood pressure was 125 systolic and 70 diastolic. The firm, irregular liver edge was palpable 4 cm. below the costal margin. The spleen could not be felt. No other abdominal masses were palpated. It was impossible to carry out any adequate neurological examination, but no gross abnormality was noted.

*Laboratory data.* The urine showed a trace of albumin, a few white and red blood cells. The Bence-Jones protein test was negative. Hemoglobin, 70 per cent; red blood cells, 2,900,000; white blood cells, 4,800 with 8 per cent myelocytes, 14 per cent non-segmented, and 52 per cent segmented polymorphonuclear leucocytes; 18 per cent lymphocytes, 8 per cent monocytes. Color index 1.2. Cell volume 28 per cent. Red cell diameter greater than 8 micra. Icterus index 16. Blood urea nitrogen, 11 mg. per cent; blood protein, 5.8 per cent; 3.8 per cent albumin; 2.0 per cent globulin. Phosphatase 54 King-Armstrong units. The bone marrow was found by the hematologic consultant to show marked increase in erythroblasts and megaloblasts, "as seen in pernicious anemia and some other types of hyperchromic anemia."

*Course.* The patient remained extremely ill. The temperature fluctuated irregularly between 97° and 104°F. Subsequent blood studies were carried out, repeatedly showing moderate macrocytic anemia. The white blood count remained low (3,400 to 5,100); the monocytes were increased, however, on one occasion as high as 21 per cent. The eosinophiles never numbered more than 1 per cent of the total white blood count. Despite treatment with liver extract and blood transfusion, no reticulocyte rise occurred. She became progressively weaker. Nine days after admission the lower extremities became edematous, the abdomen distended, with signs of free fluid in the peritoneal cavity. The temperature rose to 105°F. The patient died eleven days after admission to the hospital.

*Necropsy findings.* *Dr. Klemperer.* A huge mass of fused peri-aortic lymph nodes showed a considerable amount of fibrosis. The other lymph nodes were not grossly altered. Microscopic examination disclosed extensive typical cellular infiltration of the grossly involved nodes with Hodgkin's granuloma; the lymph nodes examined which were not grossly involved revealed fibrotic involution. The spleen was enlarged, weighing 390 grams. On section, there were many irregularly outlined grayish-yellow nodules, and hemorrhagic areas which, on histologic examination, were seen to consist of Hodgkin's granuloma surrounded by hemorrhages. The splenic vein was infiltrated by a nodule of Hodgkin's granuloma, which extended into the lumen. The liver, on section, showed exaggeration of the lobular markings, due to granulomatous infiltration of the periportal areas. The gall-bladder was filled with small stones. Bone marrow showed patches of infiltration with Hodgkin's granuloma and, microscopically, many megaloblasts within the uninvolved areas. Histologic examination of the stomach revealed very striking mucosal atrophy. The post-mortem examination of the bone marrow confirmed the findings of the bone marrow aspiration performed previously: there was marked increase in megaloblasts. Moreover, the gastric mucosa was atrophic, as seen in pernicious anemia. Therefore, coexistent pernicious anemia cannot be ruled out, although the anatomic picture is dominated by Hodgkin's disease.

*Comment.* *Dr. A. Schifrin.* I had the opportunity to observe this patient who long presented a fever of unknown origin. Pernicious anemia could have explained the blood picture, were it not for the lack of response to liver therapy. The disappearance of the transient enlarged lymph node in the neck was a reason for rejecting the diagnosis of Hodgkin's disease, to which suspicion had been directed by the presence of a prolonged obscure fever.

*Dr. Baehr.* The clinical evaluation of liver therapy for pernicious anemia is generally reliable, but not in the presence of a complication, as in this instance. Any debilitating disease, as Hodgkin's disease, and any complicating infection

may accelerate the development of pernicious anemia and render the condition completely refractory to liver therapy. It is, therefore, my opinion that this patient had both a deficiency hyperchromic anemia (pernicious anemia) and Hodgkin's disease. Another interesting feature is the presence of myelocytes in the blood; this was correctly interpreted as indicating bone marrow involvement by some disease process.

This case represents one of the best examples we have had of Hodgkin's disease which was clinically localized to the abdominal cavity.

Reported by *Edward B. Grossman, M.D.*

*Wednesday, November 27, 1940*

**Carcinoma of Bronchus Without Pulmonary Symptoms Which Extended Into the Esophagus and Produced the Symptoms and Findings of a Carcinoma of the Esophagus. Correct Diagnosis Made by Biopsy**

*[From the Medical Service of Dr. George Baehr]*

*History* (Adm. 461567; P.M.11629). A 46 year old physical training instructor had enjoyed good health until four months before admission to the hospital. He then noticed a dull, aching pain in the left upper quadrant of the abdomen appearing one to two hours after meals, and relieved by intake of food. His family physician made a diagnosis of peptic ulcer, despite negative findings on x-ray examination of the gastro-intestinal tract. After two weeks treatment by bed rest and the usual Sippy regimen, the symptoms subsided. Three weeks before admission he again began to complain of pain which was localized under the lower portion of the sternum and radiated around the left side of the chest to the back. The therapeutic measures which had succeeded previously did not result in remission of symptoms on this occasion. He became nauseated and began to vomit small amounts of a greenish fluid. The pain persisted. The patient became weaker and lost fifteen pounds in weight.

*Examination.* Examination revealed an asthenic man who did not look particularly ill. The skin and mucous membranes were not remarkable. There was no lymphadenopathy. The lungs were clear throughout. The cardiac findings were not noteworthy. The abdomen was rather tensely held but there were no tender areas, and no masses were palpable. The impression was either a gastric or esophageal ulcer.

*Laboratory data.* Urine examination revealed no noteworthy abnormality. Blood: Hemoglobin 88 per cent; white blood cells 17,350 with 74 per cent segmented polymorphonuclear leucocytes and 10 per cent non-segmented forms. Blood sedimentation time was 1½ hours. Blood urea nitrogen 8 mg. per cent. Stools were clay colored and gave a 2 plus guaiac reaction. Fractional gastric analysis after Rehfuess test meal showed no free hydrochloric acid. Blood was present in all specimens. Roentgen examination after barium meal showed a marked filling defect in the esophagus at the junction of the middle and the lower third. The defect was approximately three inches in length and was associated with narrowed lumen and, in addition, what appeared to be a mass. The stomach and duodenum were not abnormal.

*Course.* Three days after the patient was admitted to the hospital, he developed dysphagia to solid food. Esophagoscopy was performed. Thirty-two centimeters from the upper incisor teeth a grayish necrotic mass was seen occluding the lumen. The specimen

removed for biopsy was reported as necrotic tissue containing a small fragment infiltrated by tumor, probably immature squamous cell carcinoma. A surgical consultant considered the patient's excellent condition justification for operative intervention, even though it was probable that regional lymph node metastases were present.

Because of the extensive necrosis of the first specimen obtained, a second esophagoscopy biopsy was deemed advisable. The pathologic report on this was "fragment of esophageal mucosa with underlying submucosa, and muscularis, latter infiltrated by small cell carcinoma. Mucosa intact. Carcinoma of bronchus should be excluded." Bronchoscopy was, therefore, carried out with no abnormal findings. X-ray examination of the chest showed slight exaggeration of the pulmonary markings at the left base. In the lateral position there was no evidence of enlarged lymph nodes, but an irregular density was present in the posterior mediastinum above the diaphragm. Because of the opinion of the pathologist that the lesion was extra-esophageal in origin, it was believed that esophagectomy offered little hope.

Three weeks after admission the patient became much more ill than he had been up to that time. His temperature, which had previously been normal, gradually rose to 103°F. He began to cough and to complain of pain in the right side of the chest, aggravated by respiratory movements. Dullness and moist râles appeared over the right lower lobe. X-ray examination of the chest now showed irregular infiltration in both lower lobes, more marked on the right, extension of the hilar shadows on the right side, and pleural thickening over the right base. The sputum became purulent and the breath developed a foul odor. The down hill course was accelerated; weakness and cachexia became marked. The patient lapsed into coma and died one month after admission to the hospital.

*Necropsy findings.* Dr. Klemperer. The lower portion of the *esophagus* was the site of a huge crater in an ulcerated tumor mass which was adherent to the medial surface of the *right lung* and to surrounding tumor masses. Within the posterior and medial portion of the lower lobe of the right lung was a large cavity containing necrotic putrid material, excavating lung and tumor mass. A branch of the paravertebral bronchus was completely occluded by tumor. The pulmonary cavity communicated with the esophagus through an irregular perforation. Histologic examination revealed small cylindrical-cell carcinoma of the bronchus, which invaded the esophagus from without. The *liver* contained innumerable metastases, measuring from 2 mm. to 4 cm. in diameter. Metastases from the carcinoma of the bronchus were also present in the *adrenal glands*.

*Comment.* Dr. Baehr. This patient had a bronchial carcinoma which produced no symptoms whatever until it invaded the esophageal wall. The first symptoms were the result of esophageal obstruction and both the clinical observations and the x-ray and esophagoscopy findings warranted a diagnosis of primary carcinoma of the esophagus. It was Dr. Otani who astutely interpreted the microscopic picture of the esophageal biopsy as indicating the existence of an extra-esophageal neoplasm arising primarily in a bronchus, even though there were no symptoms and as yet no x-ray evidence of pulmonary disease.

Reported by Edward B. Grossman, M.D.

Wednesday, January 10, 1940

### Massive Embolization of Renal Glomeruli in Subacute Bacterial Endocarditis. Death in Azothemia

[From the Medical Service of Dr. B. S. Oppenheimer]

*History* (Adm. 462359; P.M. 11640). This was the first admission of a 33 year old man who gave a history of fever of five months' duration. At the age

of 13 years he had had scarlet fever, at which time a diagnosis of heart involvement was made. At that time he had ankle edema for a year. He experienced dyspnea and palpitation only on running up stairs. Five months before admission he developed an upper respiratory infection with pain in the small of the back and slight fever. A diagnosis of "grippe" was made. He became ambulatory after several days of bed rest, but the fever still continued and after a month he was again put to bed. Night sweats and daily rises in temperature to 102°F. persisted. Hematuria was discovered. Sulfanilamide was administered for six weeks. He was admitted to another institution where a work-up revealed normal cystoscopic findings but a blood culture was positive for streptococcus viridans. Two months prior to admission to this hospital there was a large brown spot before the right eye which gradually disappeared within a week. No embolic phenomena were noted. There was a weight loss of 23 pounds and the patient complained of weakness.

*Examination.* The patient was well developed, poorly nourished, appearing chronically ill. Scattered white-centered petechiae were seen on the trunk and upper arms. The pupils were normal. There were several conjunctival petechiae. The fundi showed bilateral papilledema and several Roth spots. The oral mucous membrane was pale. The neck veins were not distended. The lungs were normal. The heart was not enlarged, and the sounds were of good quality. A loud, high pitched systolic murmur was heard over the mitral area and transmitted over the precordium into the axillae and back. P2 was louder than A2. The rhythm was regular. The blood pressure was 122 systolic and 68 diastolic. The liver was felt three fingers below the costal margin. An Osler node was present on the right middle finger. There was no clubbing of the fingers or toes. Neurological examination was negative. The impression was that of subacute bacterial endocarditis.

*Laboratory Data.* Blood: hemoglobin, 61 per cent; red blood cells, 3,300,000; white blood cells, 10,000 with 85 per cent polymorphonuclear leucocytes; sedimentation time, 35 minutes; blood culture on admission, positive for streptococcus viridans, as were all four subsequent examinations; Wassermann reaction, negative; sugar, 100 mg. per cent; urea nitrogen, 18; chlorides, 750 mg. per cent. Icterus index, 2. Prothrombin time was normal. Congo-red test showed 35 per cent retention. Chest x-ray examination showed generalized cardiac enlargement. Electrocardiogram showed slurring of QRS and low T waves. Random specimens of urine concentrated to 1016, contained 2 to 3 plus albumin, 6 to 8 red blood cells, 4 to 6 white blood cells, occasional granular and cellular casts. Esbach determination showed an excretion of 2 grams of albumin per liter. Urine concentration test showed fixation of specific gravity at 1010, although random specimens showed readings up to 1016. Cerebrospinal fluid examination was negative. Blood smear showed no macrophages.

*Course.* The diagnosis was clear in view of the persistent elevation of temperature, heart findings, splenomegaly, urinalysis and the positive blood culture. Before beginning therapy, several badly infected teeth were removed and culture from their apices showed staphylococcus albus and streptococcus viridans. The patient was started on sulfapyridine in full dosage. This was poorly tolerated as it provoked considerable nausea and vomiting. The temperature fell, but after a period of three days, it again became elevated and remained so. Sodium sulfapyridine was given parenterally but this was also stopped in a few days. Ten days after admission the patient became irrational and somewhat somnolent. Examination now revealed spontaneous twitching of the left side of the face, left central facial weakness, left hemiparesis and a left Babinski sign. It was felt that this was the result of cerebral embolization. At this time there were numerous, generalized petechiae, many with white centers; the tourniquet test was positive. In spite of a transfusion, the hemoglobin continued to fall. Bilateral costo-vertebral angle tenderness developed. Be-

cause of the mental retardation and somnolence, the blood urea nitrogen was checked and found to be 156 mg. per cent. This was rather surprising in view of the fact that there was no uriferous odor to the breath, apparently adequate amounts of urine were being passed, and the blood pressure was 106 systolic and 70 diastolic. A check of the laboratory finding again showed an elevation to 116 mg. per cent. Two days later, there were present all the unmistakable features of uremia. A loud pericardial friction rub became audible. The blood phosphorus rose to 7.3 mg. per cent; the calcium was 9.3 mg. per cent. The picture was attributed to extensive renal infarction. He declined rapidly and died four weeks after admission.

*Necropsy Findings.* Dr. Klemperer. The heart showed classical evidence of the presence of subacute bacterial endocarditis. The mitral valve contained small but extensive vegetations on the free edges; the lesions also extended downward to involve the chordae. These were thickened and indicated an old rheumatic process. The vegetations extended upwards to involve the posterior wall of the left auricle in the region of the MacCallum lesion. The aortic valve cusps also showed bacterial vegetations, as well as evidences of preceding rheumatic endocarditis.

The kidneys had the mottled appearance indicative of destruction of the renal parenchyma and subsequent fibrous replacement. Many petechial hemorrhages were present but there was only one relatively small infarct. On cross section the cortical markings were indistinct and many gray areas of fibrosis could be seen. Microscopically there was generalized involvement of the glomeruli. The lesions were of different ages and affected only portions of the involved glomeruli, in a manner commonly seen in the kidneys during the active phase of subacute bacterial endocarditis.

The spleen was enlarged, weighing 310 grams and contained many large, anemic infarcts. The brain had evidences of cerebral embolization. There was a recent uremic pericarditis.

This is a typical case of subacute bacterial endocarditis. The interesting feature is the massive focal glomerular embolization which produced the same general effect on renal function as a diffuse glomerulonephritis.

*Comment.* Dr. Bachr. In a study of cases in the bacteria-free stage of subacute bacterial endocarditis, it was found that one-third of the cases died in uremia, presumably a result of diffuse glomerulonephritis. Lande and I, however, came to the conclusion that all but one case actually had massive glomerular embolization, with the glomeruli showing all stages of embolization.

This case is a classic example. Such cases can be distinguished pathologically and strongly suspected clinically by the presence of massive showers of petechiae. In this case there were showers of innumerable white-centered petechiae which should have aroused the suspicion of renal insufficiency on this basis.

Reported by Max Ellenberg, M.D.



Dr. Charles H. May

## Charles H. May

August 7, 1861–December 7, 1943

Charles Henry May, son of Henry May and Henrietta Oppenheimer May, was born in Baltimore, Maryland. When he was four years old the family moved to New York where he attended private and public schools and spent two years at the College of the City of New York. After special courses in chemistry, he entered the College of Pharmacy of the City of New York from which he was graduated at the head of his class in 1879 with the award of a gold medal. In 1883 he received his degree of Doctor of Medicine at the College of Physicians and Surgeons, Columbia University and won the first Harsen prize for clinical reports and the first Harsen prize for efficiency. He was offered a position at Bellevue Hospital but declined since he had already accepted an appointment at The Mount Sinai Hospital.

After leaving The Mount Sinai Hospital Dr. May entered private practice. While in general practice he worked with Seguin in nervous diseases, Delafield in internal medicine and Agnew in ophthalmology. It was Dr. Agnew's friendship and kindness that influenced him to specialize in ophthalmology.

In 1887 Dr. May went to Europe for post-graduate study. He spent six months at Halle studying the eye and ear and six months at Vienna working in the clinics of Fuchs, Dimmer, Koenigstein, Politzer and Urbanschieht. On his way home he visited clinics in Paris and London. In 1888 he resumed practice in New York, specializing at first in both otology and ophthalmology. Appointment to Manhattan Eye and Ear Hospital, Herman Knapp's Hospital and College of Physicians and Surgeons followed. He was also associated with the Polyclinic Hospital. At the College of Physicians and Surgeons he became chief of clinic following the resignation of John E. Weeks. At The Mount Sinai Hospital he was made assistant attending in the Eye Department in 1893 and became full attending when Gruening retired. He was Attending Ophthalmologist for 14 years and Consulting Ophthalmologist for 20 years. In 1914 he established the eye service at Bellevue Hospital where a ward of forty-five beds was equipped according to his plans. He was director of this service until 1925 when he resigned to be succeeded by John M. Wheeler. Later he was Consulting Ophthalmologist to The Mount Sinai, Bellevue, French and Monmouth Memorial Hospitals.

Dr. May contributed considerably to medical literature. His best known work is his "Manual of Diseases of the Eye". The book appeared in 1900 and has been in wide use as a textbook for medical students and general practitioners of medicine. It has been translated into many languages, the most recent one being Portuguese. He took great pride in this work, ever seeking to keep the book up to date. Just two weeks before his death, he insisted on correcting the proof for the eighteenth edition.

He was one of the first in this country to report in 1899 a case of restoration of the conjunctival cul-de-sac in total symblepharon by means of Thiersch skin

graft and in 1901 the restoration of a socket by a large Wolff graft. He wrote on the prevention and treatment of ophthalmia neonatorum in 1895, in 1906 and in 1908.

Early in his career he compiled a textbook for grammar schools on anatomy, physiology and hygiene published by William Wood, which went through four editions. He also published an index to *Materia Medica* which he wrote with Charles F. Mason. He wrote a manual of the Diseases of Women which he published in 1885. He also wrote on ophthalmic subjects for the "International Encyclopedia", the "Reference Handbook of the Medical Sciences" and for a number of lay journals.

In 1900, Dr. May introduced an electric ophthalmoscope based on a new principle of illumination. The advantages of the new instrument were indestructibility, the employment of a solid prism reflector instead of a mirror and a condensing lens which gave an even illumination of the fundus devoid of shadow and reflexes so annoying in the older instruments. The system of illumination in the May Electric Ophthalmoscope is now in general use.

His hobbies were the enjoyment of fine cigars, cravats and summer travels in Europe. He crossed the Atlantic every summer for many years, making in all fifty-four trips.

His practice was extensive and lucrative. He was loved by his patients and particularly by doctors for whom he saw cases in consultation. He had a vast experience and keen insight and was always helpful.

He was a member of the American Ophthalmological Society, The American Academy of Ophthalmology and Otolaryngology, The New York Academy of Medicine, The American College of Surgeons and The New York State and County Medical Societies.

He is survived by his widow, Mrs. Rosalie Allen May and two sisters, Mrs. Florence Oppenheimer and Mrs. Nellie Mosbacher. One month before his death, Dr. May and his wife celebrated their fiftieth wedding anniversary.

The name, Charles H. May, is universally known to the medical profession. His life was rife with achievements and he made many valuable contributions in his chosen field of medicine. He was a great scholar and teacher, a fine clinician and an excellent surgeon. The profession has lost one of its most distinguished ophthalmologists.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

### *III. Diagnosis of Female Sterility.* I. C. RUBIN. *Western J. Surg., Obst. & Gynec.* 50: 349, July 1942.

Those procedures should be employed that have a definite purpose supported by practical experience. In general emphasis is placed on the following steps in the inquiry: (1) a complete medical history especially detailed in the sphere of genital function and the constitutional state; (2) general physical examination with particular reference to that of the genitals and secondary sex characters; (3) the Huhner test and if necessary examination of the unmixed semen; (4) urinalysis, blood examination including serologic tests for syphilis; (5) nonoperative tests for tubal patency; (6) basal metabolic rate determination; and (7) in individual cases, as the indications arise, further investigation by means of specialized tests including serologic, hormonologic, roentgenologic and biochemical.

The clinical appraisal of the patient including her psychic peculiarities, domestic happiness, dietary habits and sex habits underlying her inability to conceive must continue to receive first consideration while laboratory methods judiciously applied as in other fields of medicine may serve as useful aids.

### *The Angiocardiographic Demonstration of an Arteriovenous Fistula.* M. F. STEINBERG, A. GRISHMAN AND M. L. SUSSMAN. *Surg., Gynec. & Obst.* 75:93, July 1942.

Angiocardiography is a simple, effective procedure for the precise localization of arteriovenous fistulas involving large vessels near the heart. It is especially valuable in cases involving those vessels which otherwise would require a difficult surgical exposure to perform arteriography.

### *Uric Acid Partition in Gout and in Hepatic Disease.* D. ADLERSBERG, E. GRISHMAN, AND H. SOBOTKA. *Arch. Int. Med.*, 70: 101, July 1942.

The non-ultrafiltrable (bound) uric acid as compared to the total uric acid content of the serum was studied in normal subjects and patients with miscellaneous pathologic conditions. Comparatively constant uric acid partition was found as a characteristic of the normal blood serum. Among the pathologic conditions considered particularly gout and hepatic damage bring about disturbance of the uric acid partition, characterized by a diminution of the free, and elevation of the bound uric acid fraction. The role of the liver in purine metabolism is discussed.

In 10 patients with gout, elevation of total and correspondingly of bound uric acid prevailed. Gout with extreme hyperurecemia may be associated with a normal uric acid partition, on the other hand, patients with gout in whom the total uric content is not elevated may be distinguished by a high bound uric acid ratio. The diagnostic significance of such findings is suggested.

### *Granulomatous Jejuno-Ileitis.* M. L. SUSSMAN, AND E. WACHTEL. *Radiology*, 39: 48, July 1942.

An analysis of 23 cases of granulomatous jejuno-ileitis is presented from clinical, pathologic, and roentgenologic points of view. This disease appears most frequently in late

adolescence or early adult life. It is characterized clinically by diarrhea and abdominal pain, although fever appears during the course of the disease in most cases. There is a distinct tendency to chronicity with varying grades of activity. Roentgenologically, differentiation from a deficiency pattern is difficult in the acute phase, but the chronic disease is characterized by rigidity and stenosis, which occasionally gives rise to obstruction.

*Pruritus Ani, with Special Reference to Therapeutic Tattooing with Mercury Sulfide.* R. TURELL. New York State J. Med. 42: 1335, July 1942.

The successful employment of tattooing of the anal canal and the perianal region with mercury sulfide for intractable anal pruritus had made it desirable to review the problem of pruritus ani in detail, so that the place of this new therapeutic measure in the general scheme of things may be evaluated.

The physiologic behavior of the apocrine sweat glands is discussed. The roles played by systemic disease, psychic factors, anal hygiene, anal lesions and dermatologic lesions are evaluated. The general and local therapeutic measures are discussed in detail as is every phase of tattooing of the anal region with mercury sulfide. The author concluded that when simple measures fail to control anal pruritus, more radical therapeutic methods (perianal subcutaneous alcohol injection, tattooing, etc.) have to be employed. In his experience, tattooing of the anal and perianal regions with mercury sulfide is an effective therapeutic measure for the properly selected, refractory cases of pruritus ani.

*Metastatic Tumors of the Brain.* J. H. GLOBUS AND T. MELTZER. Arch. Neurol. & Psychiat., 48: 163, August 1942.

The clinical manifestations and the anatomic observations in 57 cases of metastatic tumor of the brain are analyzed.

On the clinical side, observations on the evolution of the symptoms and signs in cases of metastatic tumor of the brain point to the following conclusions:

The onset of cerebral manifestations is most commonly acute and often precipitate, with symptoms of increased intracranial tension, such as headache, nausea and vomiting. These symptoms, appearing early in the disease, manifest themselves in an intensity out of proportion to the then present meager objective neurologic signs.

Papilledema is absent in a large number of instances (34 cases, or 59.6 per cent, in this series); moderate in some (16 cases, or 28 per cent), and pronounced only in a few (7 cases, or 12 per cent).

The presence or absence of meningeal signs does not seem to bear any relation to the position of the tumor in the brain.

Mental alterations are found in a somewhat greater number of cases of metastatic than of primary tumor of the brain (23 cases in this series).

The evolution of the clinical course is characterized by a rapid transition from the early stage, in which the cerebral signs are few and vague, to a stage in which manifestations of an existing focal lesion of the brain are prominent. In a large number of instances these may be of a disseminated character, and in an equal number of instances they may point to the presence of a single circumscribed process. The rapid unfolding of the clinical picture is marked by an equally rapid decline in the general condition of the patient.

The laboratory investigations pertaining to the cerebrospinal fluid contribute little to the diagnosis. While the cell count of the cerebrospinal fluid at times may be above normal, or even very high, tumor cells are rarely discovered in the fluid. The increase in the globulin and the slight increase in the sugar content of the cerebrospinal fluid noted in a few cases are not pathognomonic of metastasis.

Thus, it may be said that an acute onset of symptoms of increased intracranial tension, such as headache and vomiting, followed by rapidly progressive development of neurologic signs of either disseminated or more localized character, accompanied by slow development of papilledema in the absence of positive serologic reactions and febrile manifestations, points strongly to an expanding lesion of a metastatic character. Such a suspicion demands

search for a primary lesion by all available clinical and laboratory methods, since the therapeutic indications depend on recognition of the character of the neoplastic process.

In spite of its invasive character, a discrete line of demarcation between the metastatic tumor and the adjacent tissue is maintained, and only mild reactive changes, such as a narrow zone of condensation, gliosis and occasional lymphocytic infiltration in nearby brain tissue, are present. In rare instances a narrow belt of hemorrhage is observed, and this is particularly true of metastases from the so-called Grawitz type of tumor, or hypernephroma. Relatively wide areas of edema of surrounding brain tissue are common.

The tumor tissue itself is usually rich in blood vessels, occasionally shows extravasation but most frequently contains relatively large areas of necrobiosis. A fairly large number of such tumors contain cysts filled with gelatinous material. In a small group of cases of metastatic invasion of the brain the lesions are widespread in distribution but are restricted to infiltrations about blood vessels. These lesions are recognized only microscopically and are occasionally described as miliary carcinomas.

The choroid plexus, which was studied with a view to determining its role in the transportation of tumor cells to the nervous system, was the seat of metastatic invasion in only 1 of 57 cases.

### BOOK REVIEW

SYLVAN D. MANHEIM, M.D. *Proctology*. Oxford Univ. Press, New York, 1943.

The author has assembled in outline form a complete discussion of diseases of the anus, anal canal and rectum. As such, the book should be of great value for students and the general practitioner who treats anal fissure, ulcer, hemorrhoids, pruritus ani and allied conditions. They will find there a detailed description of the therapy of these ailments. Thus, for example, the injection treatment for hemorrhoids is given, step by step. The much discussed tattoo treatment for pruritus ani will be of interest to those unfamiliar with this technic. Surgical procedures are also given in great detail, including types of anesthesia, postoperative care and methods of choice. Congenital malformations, cryptitis and papillitis and the fine points in the management of anorectal abscess and fistula are fully described. Other topics of interest include melanosis coli, lymphopathia venereum, factitial proctitis and management of a permanent colostomy. There are many other valuable features, including a clear exposition of the anatomy of the anorectal region, the practical aspects of which are emphasized. The author has really succeeded in giving the reader in concise fashion a full understanding of the fundamental principles of proctology. This valuable addition to the Oxford medical outline series is highly recommended.

ALBERT CORNELL.

## NOTE

In order to avoid duplication in indexing articles appearing in this Journal, attention is called to the fact that the following papers have been previously published at greater length here and elsewhere:

"Subacute Streptococcus Viridans Endarteritis Superimposed on Patent Ductus Arteriosus. Recurrence After 12½ Years. Recovery after Operation" by Dr. Arthur S. W. Touroff, J. Mt. Sinai Hosp. 10: 729, 1944, originally appeared in Am. Heart J. 23: 857, 1942 with Dr. L. R. Tuchman as co-author.

"Constrictive Pericarditis. Classic Type with Pericardiectomy" by Dr. Charles K. Friedberg, J. Mt. Sinai Hosp. 10: 717, 1944 was reported, among other cases, in an article entitled "Chronic Constrictive Pericarditis; Medical and Surgical Aspects" by Dr. B. S. Oppenheimer, Dr. William M. Hitzig and Dr. Harold Neuhof, in J. Mt. Sinai Hosp. 7: 270, 1941.

## CORRECTION

In the article by Irving R. Roth, M.D. entitled "The Community Cardiac Program and the Role of the Modern Cardiac Clinic", which appeared in the Journal of The Mount Sinai Hospital, Vol. 10, No. 5 (January-February) 1944, in the last sentence of the third paragraph the word *positive* should read *possible*.

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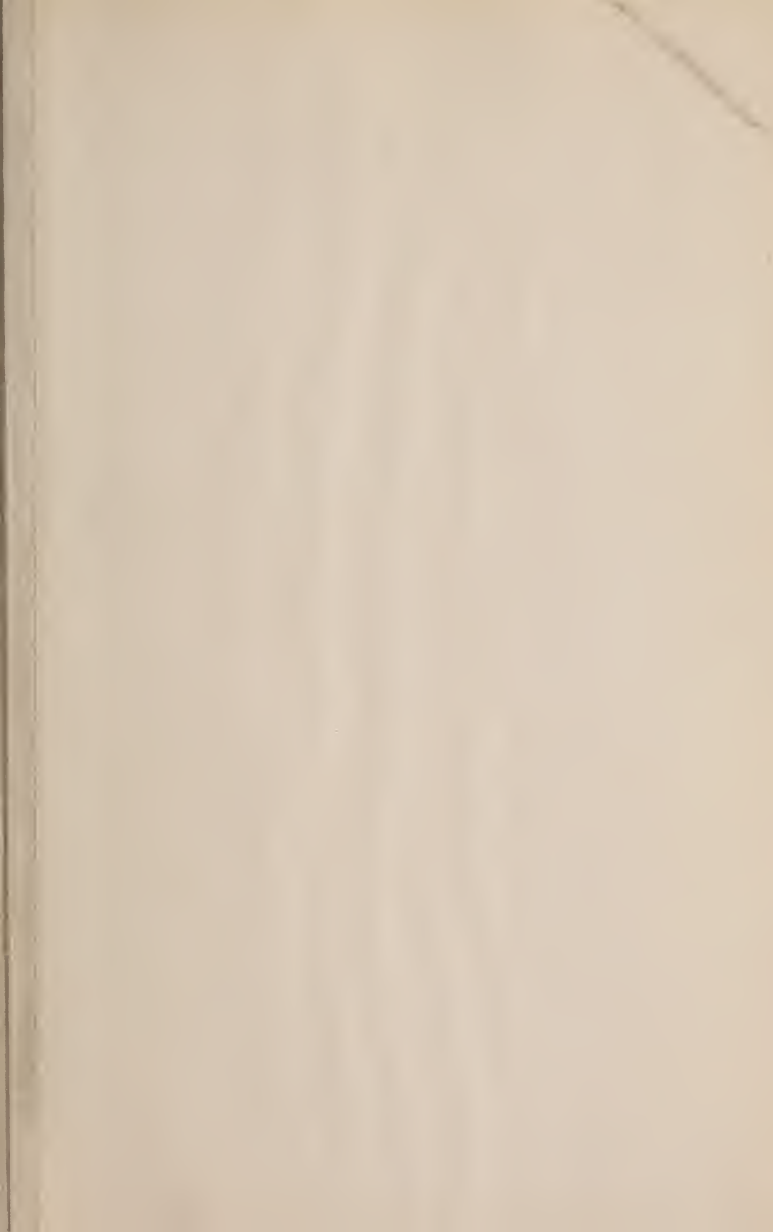
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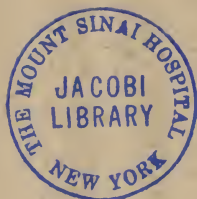
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